Research Paper

Comparison between physical and cognitive treatment in patients with MCI and Alzheimer's disease

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ABSTRACT

Cognitive and physical activity treatments (CT and PT) are two non-pharmacological approaches frequently used in patients with Mild Cognitive Impairment (MCI) and Alzheimer's Disease (AD). The aim of this study was to compare CT and PT in these diseases. Eighty-seven patients were randomly assigned to CT (n=30), PT (n=27) or control group (CTRL; n=30) for 6 months. The global cognitive function was measured by Mini Mental State Examination (MMSE). Specific neuropsychological tests explored attention, memory, executive functions, behavioral disorders. Cardiovascular risk factors (CVD) were collected. All measures were performed before (T0), after treatments (T1), and at three-months follow-up (T2). MMSE did not change from T0 to T1 and T2 in patients assigned to PT and CT, while CTRL patients showed a decline MCI: -11.8%, AD: -16.2%). Between group differences (MCI vs AD) were not found at T1 and T2. Significant worsening was found for CTRL in MCI (T0- T1: *P*=.039; T0-T2: *P*<.001) and AD (T0-T1: *P*<.001; T0-T2: *P*<.001), and amelioration was found for CT in AD (T0-T2: *P*<.001). Attention, executive functions and behavioral disorders were unaffected by either PT or CT. Memory was increased in patients with MCI assigned to PT (+6.9%) and CT (+8.5%).. CVD were ameliorated in the PT group. CTRL patients of both groups, revealed significant decline in all functions and no between groups differences were detected. PT appear to ameliorate CVD. Although between groups differences were not found, results suggest a major retention in MCI compared with AD, suggesting that the latter might benefit better of constant rather than periodic treatments. This study confirms the positive effects of CT and PT in mitigating the cognitive decline in MCI and AD patients, and it is the first to demonstrate their similar effectiveness on maintaining cognitive function.

INTRODUCTION

In 2050 the number of people aged ≥60 years will increase by 1.25 billion [1] with an estimate of 115.4 million of persons with dementia [2]. Alzheimer's disease (AD) is the cause of 60–70% of dementia, affecting 48 million of people worldwide [3], causing severe clinical, social, and economic problems [1].

AD is characterized by intraneuronal fibrillary tangles and extracellular deposit of amyloid plaques (Aβ) coupled with reactive microgliosis, loss of neurons and synapses in the cortex [4]. Deposits of Aβ can lead to cortical dysfunctions resulting in many cognitive impairments such as memory and intellectual disabilities, causing a decline in activities of daily living and interfering with quality of life [5]. Although current pharmacological treatments may improve symptoms, there are no disease-modifying strategies for AD and new non-pharmacological interventions are needed [6].

Individuals with Mild Cognitive Impairment (MCI), which show cognitive changes greater than expected for an individual's age and education level but do not interfere with daily-life activities, have increased risk of dementia. The estimated global prevalence of MCI is 9.6–21.6% [7, 8]. Pharmacological treatments for MCI have modest to no effect, and new therapeutic approaches are needed in this condition [9]. Cognitive stimulation is the most recommended non-pharmacological approach for cognitive symptoms in MCI and mild-to-moderate dementia. Despite these promising results, the evidence for cognitive training is still preliminary [10].

Physical activity treatment (PT) is another non-pharmacological treatment with some efficacy in dementia [11, 12]. The potential of PT to attenuate the cognitive decline in healthy elderly is clear [13], but the effects of PT on cognitive decline is less consistent because of methodological limits, such as different exercise interventions and small sample size. A systematic review [14] showed that aerobic and resistance PT had some positive effects on global cognition, executive functions, attention and delayed recall in MCI and no cognitive effects in AD. Other studies indicated that PT improve global cognitive ability and memory in MCI [15]. PT was reported to delay the cognitive decline in persons at risk of or who have AD [12].

Unfortunately, to date these data are still unclear due to the heterogeneity between studies and outcomes [11]. Therefore, further research with additional and more specific neuropsychological measurements are needed. The aim of this study was to compare the effects of cognitive treatment (CT) and PT in older people with AD and in subjects with MCI. Our hypothesis was that both CT and PT would attenuate the progression of cognitive deterioration in AD and MCI, with similar results in primary outcome measure, but different effects in the secondary outcome measures. Specifically, we expected amelioration in the memory domain in CT group, while PT group would exhibit improvements in physical function and attention.

RESULTS

Demographic and clinical data

The flow diagram of the study with the specific numbers of participants is reported in Figure 1. The sample was composed of 27 MCI (11 males/16 females) and 60 patients with AD (21 males/39 females). They were randomized to the CT group (n = 30), PT group (n = 27) or the CTRL group (n = 30). Age, education, MMSE and POMA were not statistically different between the three groups of AD and the three groups of MCI at baseline. Patients' demographic and clinical characteristics are reported in Table 1. Primary and secondary outcomes measures did not significantly differ between the three groups at baseline (T0).

Primary outcomes

Significant effects of the factors Time ($F_{2,162}$= 59.327; P<.001), Treatment ($F_{2,81}$= 4.584; P=.013) and Group ($F_{1,81}$= 86.707; P<.001) and Time X Treatment interaction ($F_{4,162}$= 15.328; P<.001) on MMSE were found.

Post-hoc tests revealed no difference between the three treatments' groups at T1 and T2 both in patients with MCI and AD. However, in MCI amelioration in CTRL were found (T0- T1: P=.039; T0-T2: P<.001). In AD worsening in CTRL (T0-T1: P<.001; T0-T2: P<.001), and amelioration in CT (T0-T2: P<.001) were seen (see Figure 2).

Secondary cognitive and behavioral outcomes in MCI and AD

Significant effects of the factors Time ($F_{2,162}$= 11.444; P<.001), Treatment ($F_{2,81}$= 4.077; P=.020) and Group ($F_{1,81}$= 39.840; P<.001) and Time x Treatment ($F_{4,162}$= 10.887; P<.001) and Time x Group ($F_{2,162}$= 5.277; P=.006) interactions on FAB. Post-hoc comparisons revealed no significant results in MCI, but in AD a significant difference between CTRL and CT in T2 (P=.041). Moreover, in AD a worsening of CTRL in time (T0-T1: P<.000; T0-T2: P<.000) was found.

Effects of the factors Time ($F_{2,162}$= 29.885; P<.001) and Group ($F_{1,81}$= 38.598; P<.001) and the Time X Treatment ($F_{4,162}$= 5.032; P<.001) and Time X Treatment X Group ($F_{4,162}$= 2.575; P=.039) interactions were found on IADL. Post-hoc did not reveal any difference at T1 and T2 between the three treatments' groups in patients with MCI and in patients with AD. We found a worsening of CTRL between T0 and T2 (P<.001) in MCI, and differences from T0 to T2 in CT (P<.001) and CTRL (P<.001) in AD.

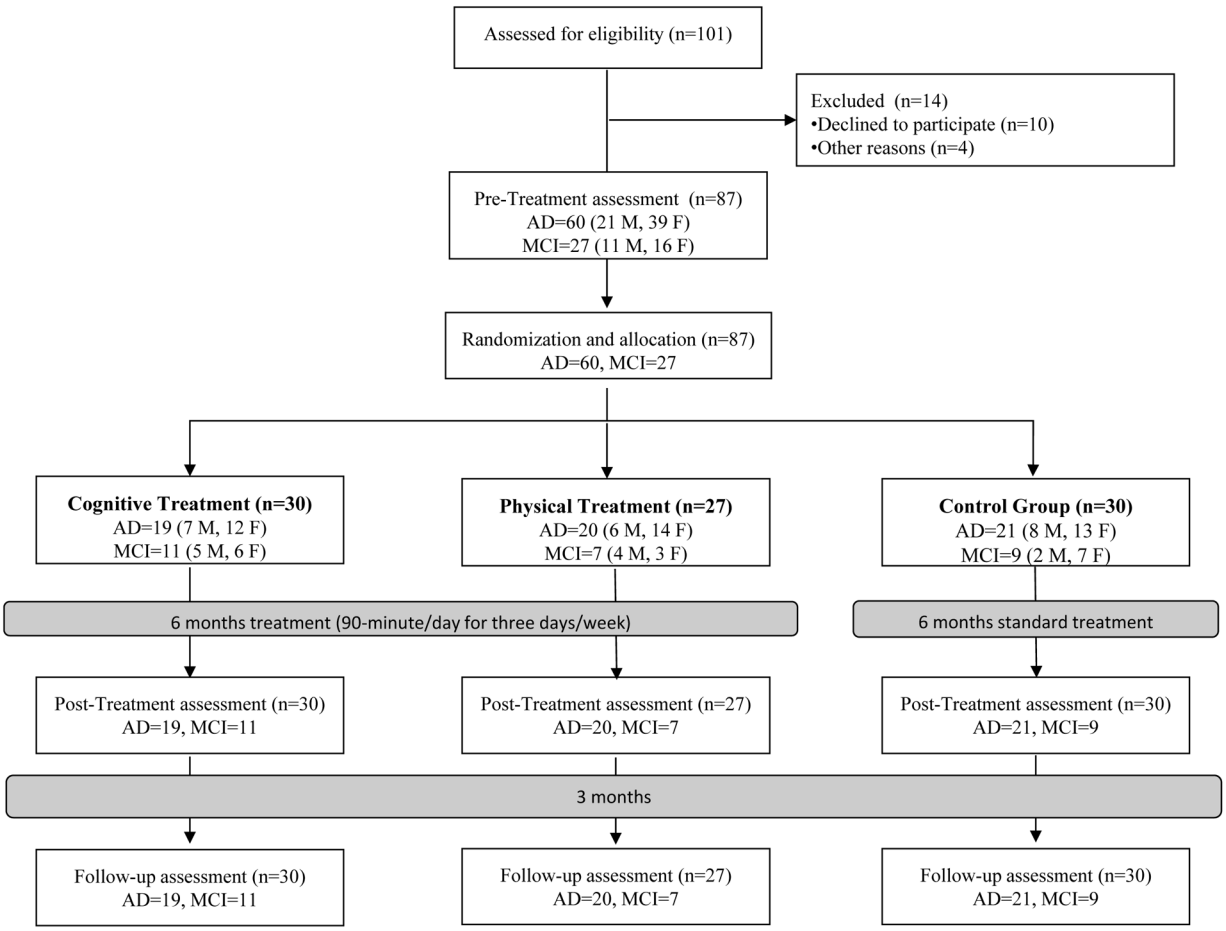

Figure 1. Flow diagram of the randomized controlled trial. Abbreviations: MCI: Mild Cognitive Impairment; AD: Alzheimer's Disease; M: Male; F: Female.

Significant effects of Time (F2,162= 18.425; *P*<.001), Treatment ($F_{2,81}$= 18.204; *P*<.001), Group ($F_{1,81}$= 15.255; *P*<.001) and Time X Treatment ($F_{4,162}$= 21.339; *P*<.001) and Treatment X Group ($F_{2,81}$= 6.605; *P*=.002) interactions on NPI. Post-hoc showed difference between groups at T1 (PT vs. CTRL: *P*<.001; CT vs. CTRL: *P*<.001) and at T2 (PT vs. CTRL: *P*<.001; CT vs. CTRL: *P*<.001) in AD. Moreover, we found changes from T0 to T2 in CTRL (*P*<.001) in MCI and worsening of CTRL across time (T0-T1: *P*=.001; T0-T2: *P*<.001) in AD (Table 2).

Secondary cognitive outcomes specific for MCI

Significant effects of Time ($F_{2,48}$= 7.33; *P*=.001), Treatment ($F_{2,24}$= 5.286; *P*=.012) and Time X Treatment interaction ($F_{4,48}$= 5.715; *P*<.001) on TMT-A. Post-hoc showed differences at T1 (PT vs. CTRL: *P*=.014; CT vs. CTRL: *P*=.040), and T2 (PT vs. CTRL: *P*=.001; CT vs. CTRL: *P*<.001). A worsening of CTRL across time was found (T0-T1: *P*=.006; T0-T2: *P*<.001).

In TMT-B, effects of Time ($F_{2,48}$= 12.46; *P*<.001), Treatment ($F_{2,24}$= 8.46; *P*=.001) and Time x Treatment ($F_{4,48}$= 11.93; *P*<.001) interaction were found. Post-hoc showed differences at T1 between PT and CTRL (*P*=.002), and CT and CTRL (*P*<.001), both confirmed at T2 (*P*<.001). A worsening of CTRL was found between T0 and T1 (*P*<.001) and T0 and T2 (*P*<.001).

Effects of Time ($F_{2,48}$= 16.88; *P*<.001), Treatment ($F_{2,24}$= 3.434; *P*=.048) and Time X Treatment interaction ($F_{4,48}$= 10.06; *P*<.001) on RBMT were found. Post-hoc tests showed differences at T1 (PT vs. CTRL: *P*=.022; CT vs. CTRL: *P*=.006) and T2 (PT vs. CTRL: *P*=.017; CT vs. CTRL: *P*=.028) and changes from T0 to T1 in all treatments' groups (PT: *P*=.019; CT: *P*<.001; CTRL: *P*=.006), and from T0 to T2 in CTRL (*P*<.001) (see Table 3).

Table 1. Demographic data.

	CT (30)		PT (27)		CTRL (30)	
	AD (19)	**MCI (11)**	**AD (20)**	**MCI (7)**	**AD (21)**	**MCI (9)**
Numbers	7♂/12♀	5♂/6♀	6♂/14♀	4♂/3♀	8♂/13♀	2♂/7♀
Age (years)	79±7	76±5	79±9	75±5	80±7	79±3
Education (years)	8±5	9±4	7±4	10±4	7±3	8±4
MMSE (0-30)	19.6±4.3	26.4±1.4	17.8±5.7	27±2.2	18.7±2.3	25.7±1.8
POMA (0-28)	22.9±3.7	25.4±2.3	22.7±2.9	26.1±2.4	23.8±3.2	24.4±3.5
CDR (0-3)	9 CDR=1	11 CDR=0.5	9 CDR=1	7 CDR=0.5	11 CDR=1	9 CDR=0.5
	10 CDR=2		11 CDR=2		10 CDR=2	
Height (m)	1.65	1.66	1.62	1.67	1.65	1.62
Weight (kg)	65.4	73.9	67.4	79.9	67.1	73.0
Resting HR (bpm)	40	59	66	59	74	65
Pharmacological treatment						
Cholinesterase Inhibitors	9	2	9	1	9	0
Antipsychotics	4	0	5	0	4	0
Antidepressants	8	4	11	3	13	1
Benzodiazepines	2	0	1	0	6	0
Comorbidity						
Hypertension	13	8	8	6	11	4
Cardiovascular diseases	10	6	5	2	8	3
Diabetes	1	3	1	3	1	3
Arthrosis	1	1	4	0	1	0

Data are given as mean ± standard deviation. Abbreviations: CT: Cognitive Treatment group; PT: Physical Treatment group; CTRL: Control Group; MMSE: Mini Mental State Examination; POMA: Performance Oriented Mobility Assessment; CDR: Clinical Dementia Rating Scale; Resting HR: Heart Rate at rest.
*= Statistically significant at $p \leq 0.05$

Secondary cognitive outcomes specific for AD

Effects of Time ($F_{2,114}$= 30.81; *P*<.001) and Time X Treatment interaction ($F_{4,114}$= 23.93; *P*<.001) were found on DCT. Within-group comparisons showed changes from T0 to T1 in PT (*P*=.002) and CTRL (*P*<.001), and from T0 and T2 in CTRL (*P*<.001).

Effects of the factors Time ($F_{2,114}$= 49.05; *P*<.001) and the Time X Treatment interaction ($F_{4,114}$= 15.48; *P*<.001) were found on ADAS-Cog, with changes in PT (T0-T1: *P*=.037; T0-T2: *P*=.005) and in CTRL (T0 to T1: *P*<.001; T0 to T2: *P*<.001).

Post-hoc did not show any difference at T1 and T2 between the three treatments' groups both in DCT and in ADAS-Cog (Table 4).

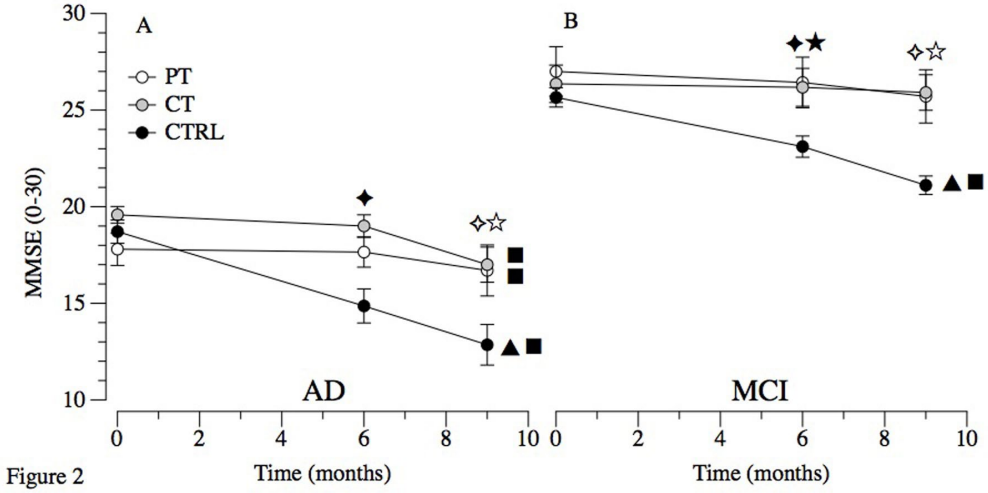

Figure 2. Primary outcome in MCI and AD. Abbreviations: MCI: Mild Cognitive Impairment; AD: Alzheimer's Disease; PT: Physical Treatment group; CT: Cognitive Treatment group; CTRL: Control Group. Within-group comparison significant results ($p \leq 0.05$): ▲ T0-T1; ■ T0-T2. Between-groups significant results ($p \leq 0.05$): ★ T1 PT vs T1 CTRL; ✦ T1 CT vs T1 CTRL; ☆ T2 PT vs T2 CTRL; ✧ T2 CT vs T2 CTRL.

Table 2. Secondary cognitive and behavioral outcomes in MCI and AD.

	Treatment	Groups	T0	T1	T2	Within-group comparison (Time)	Between-groups comparison (Treatment)
FAB (0-18)	PT	MCI	12.9±2.5	13.4±3.6	12.7±3.5		
		AD	8.9±2.4	9.9±2.4	8.5±2.8		
	CT	MCI	11.7±2	12.8±2.7	12.7±3.1		
		AD	8.6±1.9	9.1±2.3	7.7±2.9		AD: ✧
	CTRL	MCI	11.7±3	10.2±3.6	9.8±3.4		
		AD	10.3±2.6	7.3±2.9	5.3±2.8	▲ ■	
IADL (0-100%)	PT	MCI	88.2±23.6	86.4±22.1	81.8±21.2		
		AD	56.2±35.1	50.5±32.9	39.2±31.2		
	CT	MCI	84.1±19.8	89.5±18.8	86.1±19.6	■	
		AD	58.5±28.8	54.1±29.8	38.2±26.6		
	CTRL	MCI	84.4±25.9	73.1±34.3	56.4±33.8	■	
		AD	48.9±23.4	34±25.5	21.1±18.3	■	
NPI (1-144)	PT	MCI	11.7±9.1	7±4.2	9.9±5.7		
		AD	12.7±8.7	9.5±6.8	11±5.4		
	CT	MCI	10.7±7.3	6±4.9	11.4±7.9		AD: ★✦☆✧
		AD	13.6±8.9	9.6±7.1	13.7±10.4		
	CTRL	MCI	6.2±2.9	13.8±11.2	20.9±17.9	■	
		AD	16.1±8.8	29.7±9.7	40±11.3	▲ ■	

Data are given as mean ± standard deviation. Abbreviations: PT: Physical Treatment group; CT: Cognitive Treatment group; CTRL: Control group; FAB: Frontal Assessment Battery; IADL: Instrumental Activity of Daily Living; NPI: Neuropsychiatric Inventory. T0: Pre-Treatment assessment; T1: Post-Treatment assessment; T2: Follow-p assessment.
Within-group (Time) comparison significant results ($p \leq 0.05$): ▲ T0-T1; ■ T0-T2.
Between-groups (Treatment) significant results ($p \leq 0.05$): ★ T1 PT vs T1 CTRL; ✦ T1 CT vs T1 CTRL; ☆ T2 PT vs T2 CTRL; ✧ T2 CT vs T2 CTRL.

Table 3. Secondary cognitive outcomes specific for MCI.

	Treatment	T0	T1	T2		Between-groups comparison (Treatment)
TMT-A (sec.)	PT	95.6±15	82±12.2	94±17.3		
	CT	87.6±28.2	97±47.1	97.1±36.3		★✦☆✧
	CTRL	111.8±64.9	149.1±68.8	180.7±62.6	▲ ■	
TMT-B (sec.)	PT	209.1±48.7	190.1±30.6	195.7±39.8		
	CT	193.9±56.5	173.1±53.3	215.2±76.5		★✦☆✧
	CTRL	233±67.2	297.3±71	331.4±54.7	▲ ■	
RBMT (0-212)	PT	79±29.1	93.6±35.6	81.7±37	▲	
	CT	77±30.3	95.1±31.4	74.5±36.2	▲	★✦☆✧
	CTRL	66.2±22.3	51.6±25.4	38.3±21.1	▲ ■	

Data are given ad mean ± standard deviation. Abbreviations: PT: Physical Treatment group; CT: Cognitive Treatment group; CTRL: Control group. TMT: Trail Making Test; RBMT: Rivermead Behavioral Memory Test; FAB: Frontal Assessment Battery; IADL: Instrumental Activity of Daily Living; NPI: Neuropsychiatric Inventory. T0: Pre-Treatment assessment; T1: Post-Treatment assessment; T2: Follow-p assessment.
Within-group comparison significant results ($p \leq 0.05$): ▲ T0-T1; ■ T0-T2.
Between-groups significant results ($p \leq 0.05$): ★ T1 PT vs T1 CTRL; ✦ T1 CT vs T1 CTRL; ☆ T2 PT vs T2 CTRL; ✧ T2 CT vs T2 CTRL

Table 4. Secondary cognitive outcomes specific for AD.

	Treatment	T0	T1	T2	Within- group comparison (Time)	Between- groups comparison (Treatment)
DCT (0-60)	PT	25.5±11.4	29.5±10.8	25.0±10.6	▲	
	CT	23.9±9.3	25.5±7.8	22.9±10.2		
	CTRL	33.3±10.8	25.3±12.2	20.0±11.4	▲ ■	
ADAS-Cog (0-70)	PT	33.3±17.9	30.1±16.1	37.2±17.9	▲ ■	
	CT	27.1±7.6	25.5±7.5	30.1±9.2		
	CTRL	25.9±9.5	34±9.3	38.7±10.8	▲ ■	

Data are given as mean ± standard deviation. Abbreviations: PT: Physical Treatment group; CT: Cognitive Treatment group; CTRL: Control group; DCT: Digit Cancellation Test, ADAS-Cog: Cognitive section of the Alzheimer's Disease Assessment Scale; FAB: Frontal Assessment Battery; IADL: Instrumental Activity of Daily Living; NPI: Neuropsychiatric Inventory. T0: Pre-Treatment assessment; T1: Post-Treatment assessment; T2: Follow-p assessment.
Within-group comparison significant results ($p \leq 0.05$): ▲ T0-T1; ■ T0-T2.
Between-groups significant results ($p \leq 0.05$): ★ T1 PT vs T1 CTRL; ✦ T1 CT vs T1 CTRL; ☆ T2 PT vs T2 CTRL; ✧ T2 CT vs T2

Exercise capacity and cardiovascular risk factors in MCI and AD

Effects of Time ($F_{2,162}$= 5.526; *P*=.004) and Time X Treatment ($F_{4,162}$= 9.673; *P*=.040) and Time X Treatment X Group ($F_{4,162}$= 2.560; *P*=.040) interactions on BMI were seen. No between-groups differences were found in the post-hoc analysis. However, they indicated anBMI increased for CTRL in MCI (T0-T2: *P*=.008) and changes from T0 to T1 (*P*=.011) for PT in AD group.

Effects of the factors Time ($F_{2,162}$= 18.663, *P*<.001), Treatment ($F_{2,81}$= 5.322, *P*=.006) and Group ($F_{1,81}$= 10.806; *P*=.001) and Time X Treatment interaction ($F_{4,162}$= 15.487; *P*<.001) were found on 6MWT. Post-hoc analysis did not show any difference between the three treatments' groups both in AD and in MCI. We showed changes in CTRL both in MCI and in AD from T0 to T2 (*P*=.004 and *P*<.001 respectively) and from T0 to T1 for CTRL in AD (*P*<.001).

Effects of the factors Time ($F_{2,162}$= 22.53, *P*<.001), Treatment ($F_{2,81}$= 13.10, *P*<.001) and the Time X Treatment interaction ($F_{4,162}$= 26.76; *P*<.001) on systolic blood pressure were found. Post-hoc showed differences in MCI at T1 (PT vs. CTRL: *P*=.008) and in AD at T1 (PT vs. CTRL: *P*=.001) and at T2 (PT vs. CTRL: *P*=.025, CT vs. CTRL: *P*=.016). Moreover, changes in PT and in CTRL were found in MCI (PT, T0-T1: *P*=.003; CTRL, T0-T1: *P*=.041, T0-T2: *P*=.001) and in AD (PT, T0-T1: *P*<.001; CTRL, T0-T1: *P*=.002, T0-T2: *P*<.001).

Effects of the factors Time ($F_{2,162}$= 12.41, *P*<.001), Treatment ($F_{4,81}$= 4.63, *P*=.012) and the Time X Treatment ($F_{4,162}$= 24.70, *P*<.001) and Time X Treatment X Group ($F_{4,162}$= 2.69, *P*=.033) interaction on diastolic blood pressure were seen. Post-hoc showed differences between PT and CTRL at T1 both in MCI and in AD (*P*=.002, *P*=.002). A worsening in CTRL (T0-T1: *P*<.001, *P*=.001; T0-T2: *P*<.001, *P*<.001) were found both in MCI and AD. An improvement was found for PT in AD (T0-T1: *P*<.001).

Effects of Time ($F_{2,162}$= 9.520; *P*<.001), Group ($F_{1,81}$= 14.985; *P*<.001) and Time X Treatment ($F_{4,162}$= 12.581; *P*<.001) and Time X Group ($F_{2,162}$= 3.978; *P*=.020) interactions were found in glucose blood level. No between-groups differences were shown in the post-hoc analysis, but an improvement was found for PT in MCI and AD from T0 to T1 (*P*<.001, *P*=.010).

Effects of the factors Treatment ($F_{2,81}$= 3.261; *P*=.043) and Group ($F_{1,81}$= 16.672; *P*<.001) on total cholesterol, with no between-groups changes in the post-hoc analysis, but significant difference for CTRL in AD between T0 and T2 (*P*=.032) were found.

For HDL, only the Time X Treatment ($F_{4,162}$= 6.412, *P*<.001) and Time X Treatment X Group ($F_{4,162}$= 7.526, *P*<.001) interactions were significant, with neither between nor within-groups effects in the post-hoc analysis.

Effect of Time ($F_{2,162}$= 5.428, *P*=.005), Treatment ($F_{1,81}$= 36.252, *P*<.001) and Time X Treatment ($F_{4,162}$= 2.966; *P*=.021), Time X Group ($F_{2,162}$= 16.230; *P*<.001) and Time X Treatment X Group ($F_{4,162}$= 6.955; *P*<.001) interactions on LDL were found. Post-hoc analysis showed no between-groups differences, but changes in PT both in MCI and in AD (T0-T1: *P*=.015, *P*<.001).

For triglycerides, an effect of Time ($F_{2,162}$= 10.201; *P*<.001) and Time X Treatment interaction ($F_{2,162}$= 6.771; *P*<.001) were found. Post-hoc analysis did not find any difference between the three treatments' groups, but a difference for PT in AD between T0 and T1 (*P*<.001; Table 5).

Table 5. Exercise capacity and cardiovascular risk factors in MCI and AD.

	Treatment	Groups	T0	T1	T2	Within-group comparison (Time)	Between-groups comparison (Treatment)
BMI (kg/m²)	PT	MCI	28.5±4.8	27.1±4.4	27.1±4.4		
		AD	25.6±3.4	24.5±2.8	25.6±3.17	▲	
	CT	MCI	26.2±5.1	25.8±5	26±5.1		
		AD	25.8±5.5	25.6±5.3	26.2±5.5		
	CTRL	MCI	27±3.2	28±3.5	28.7±3.1		
		AD	26.9±3.1	27.4±3.3	27.6±3.4	■	
6MWT (m)	PT	MCI	391.9±57.1	447.9±73.8	398.3±69.8		
		AD	323.1±115.4	347.6±94.4	334.1±116.3		
	CT	MCI	440.1±95.4	399.7±90.9	395.9±68.9		
		AD	336±109.2	318.2±106.3	317.3±105.5		
	CTRL	MCI	352.8±55.4	314.6±44.4	285.4±29.3	■	
		AD	342.5±40.9	271±73.3	253.1±74.2	▲■	

SYS (mmHg)	PT	MCI	130.1±6.1	125.9±3	130±4.9	▲	
		AD	129.2±5	124.4±4.2	129±4.6	▲	
	CT	MCI	130.6±3.6	130.2±4.1	131.2±3		MCI: ★
		AD	128.7±6.2	128.7±6.3	128.7±6.4		AD: ★☆✧
	CTRL	MCI	135.2±11.5	138.44±9.5	139.3±9.4	▲ ■	
		AD	132.3±6	134.8±5.4	136.2±5	▲ ■	
DIA (mmHg)	PT	MCI	87.9±7.1	84.4±5.1	88.3±5.6		
		AD	87.7±3.6	84.6±2.4	87.6±2.6	▲	
	CT	MCI	88±3.7	87.1±5.1	87.4±4.2		MCI: ★
		AD	87.1±3.5	87.8±3.1	88±3.3		AD: ★
	CTRL	MCI	86.9±2.3	91.9±3.1	91.7±2.1	▲ ■	
		AD	86.6±2.1	89.2±1.2	89.4±1	▲ ■	
GLUCOSE (mg/dL)	PT	MCI	119.6±24.2	98.43±5	112.3±16.9	▲	
		AD	99.3±8.6	91±10.4	95.6±9	▲	
	CT	MCI	106±19.1	105.3±20.9	111.4±19		
		AD	98.2±12.6	97.9±13.2	97.6±13.1		
	CTRL	MCI	103±12.8	107.7±9.6	109±9.5		
		AD	96.3±13.2	98.9±12.1	98.2±11		
TOTAL CHOLESTEROL (mg/dL)	PT	MCI	167.7±16.9	135.7±9.5	161±11.3		
		AD	207.3±34.2	189±36.3	20.5±27.6		
	CT	MCI	174.9±28.2	177.5±37.5	171.2±23.1		
		AD	200.8±24.3	196.7±23.3	198.5±18.6		
	CTRL	MCI	182.9±16.4	189.4±13.9	191.2±15.1		
		AD	196.4±28.2	206.8±29.9	250.6±154.9	■	
HDL (mg/dL)	PT	MCI	63±13	68.7±10.2	57.4±16.8		
		AD	50.2±9.7	55±12.2	52.1±11.9		
	CT	MCI	58.8±21.4	57.8±15.7	52.8±10		
		AD	59.3±15.2	54±14.2	58.2±12.3		
	CTRL	MCI	57.6±9.3	53.6±11.5	63.3±8.1		
		AD	55.6±10.7	54.2±9.8	51.6±8.5		
LDL (mg/dL)	PT	MCI	90.1±14.1	105.9±14	89.7±16.3	▲	
		AD	124.8±18.7	112.2±16.6	123±20.1	▲	
	CT	MCI	94.4±12.3	100.7±12.7	98±13		
		AD	120.7±21	118.8±20.2	120.4±17.7		
	CTRL	MCI	90.8±6.4	100.1±5.4	102.3±4.7		
		AD	119.7±23.3	125.3±22.9	125.7±21.4		
TRIGLYCERIDES (mg/dL)	PT	MCI	125.4±11.7	111.6±16.4	129.7±18.7		
		AD	129.2±41	111.8±36.3	126.1±37.6	▲	
	CT	MCI	115.55±12.6	115.6±10.5	119±12.5		
		AD	118.8±37.8	125.4±37.7	127.5±36.4		
	CTRL	MCI	114.2±18.3	118.1±17.6	123.3±14.3		
		AD	124.2±22.9	128.9±25.1	132±24.4		

Data are given as mean ± standard deviation. Abbreviations: PT: Physical Treatment group; CT: Cognitive Treatment group; CTRL: Control group. BMI: Body Mass Index; 6MWT: 6-Minute Walking Test; SYS: Systolic blood pressure; DIA: Diastolic blood pressure; HDL: High-Density Lipoprotein, LDL: Low-Density Lipoprotein. T0: Pre-Treatment assessment; T1: Post-Treatment assessment; T2: Follow-p assessment.

Within-group comparison significant results ($p \leq 0.05$): ▲ T0-T1; ■ T0-T2.

Between-groups significant results ($p \leq 0.05$): ★ T1 PT vs T1 CTRL; ✦ T1 CT vs T1 CTRL; ☆ T2 PT vs T2 CTRL; ✧ T2 CT vs T2 CTRL

DISCUSSION

The aim of this RCT was to evaluate the effects of CT and PT on the progression of the cognitive deficits in MCI and AD. In agreement with our hypothesis, the natural progression of the cognitive symptoms for both MCI and AD was mitigated by CT and PT. Specifically, our results confirm the hypothesis that both treatments are successful in slowing down the usual worsening of cognitive symptoms in patients with MCI and AD. Also, secondary outcomes suggest that both treatments have positive effects on memory and attention abilities in patients with MCI. It is important to note that a general amelioration of the cardiovascular risk factors and exercise capacity were retrieved in both MCI and AD after PT. Long term effects of both CT and PT seem to persist after the end of the treatments. Although between groups differences at T1 and T2 were generally not found, results indicate that MCI retain better than AD the achieved adaptations, suggesting that the latter may better benefit from a constant rather than a periodic treatment. Overall the results of this study suggest that PT and CT have similar effectiveness in several cognitive domains and can be incorporated among the non-pharmacological treatments for patients with MCI and AD.

Impact of CT and PT on global cognitive impairment in patients with MCI

The results of this study indicate that the overall cognitive worsening (measured with MMSE) are reduced in patients with MCI undergoing CT and PT. Indeed, this study demonstrates a significant difference for both experimental treatments in comparison to the control group (Figure 2, Panel A). Interestingly, these positive effects are persistent for both CT and PT leading to long-term effects significantly detectable 3 months after the treatment ended. As expected, and previously reported by our group [16] CTRL underwent to a significant decline. The rapid decline in cognitive functioning is commonly reported in the literature that reported a loss of 3 or more points on the MMSE score in 6 months. [12, 17]. The effects of cognitive treatments in postponing cognitive decline in persons with MCI is also confirmed in a recent meta-analysis that showed memory and multidomain-lifestyle interventions to facilitate partial activation of compensatory scaffolding and neuroplasticity [18]. The effectiveness of PT were confirmed in reviews and meta-analysis [5, 12, 14, 19, 20] that showed PT, in particular aerobic exercise, to improves global cognitive scores [21-23], with a moderate but significant effect on memory [5] and executive control processes such as planning, scheduling, dealing with ambiguity, working memory and multitasking [24]. Overall, our results are highly relevant because for the first time the efficacy of a PT has been compared with a CT, and the potential integration of these successful approaches in the standard clinical scenario likely expand the possible treatments.

Impact of CT and PT on global cognitive impairment in patients with AD

The results of this study indicate that both CT and PT preserved the cognitive status in AD during the six months of treatment. Unfortunately, both groups but in particular CT exhibited a severe drop in the cognitive performance 3 months after the training (Figure 2, Panel B). This lack of long-term effects is probably due to the more severe cognitive and physical impairments of these patients, which may require continuous treatments. As expected, the global cognitive status of the CTRL group progressively worsened.

Our data are in agreement with the positive effect of CT on general cognition in AD [15]. Moreover, the positive effects of PT in our RCT are in line with several recent studies in AD [25-30]. As previously reported by our group [28, 31], it is possible to stabilize the progressive cognitive dysfunctions in nursing home residents with AD through a specific moderate intensity endurance and resistance training. These data suggest that the practice of regular physical activity might contribute to slower cognitive decline. However, ~57% of previous studies used the MMSE as the only cognitive outcome measure [32], and this may not be sensitive enough to change because it does not explore in depth any cognitive domain, and in particular the memory deficits associated with AD. The use of other cognitive outcomes in this study further supports the effectiveness of CT and PT.

Impact of CT and PT on specific cognitive domains in patients with MCI

In patients with MCI we observed that 6 months of CT or PT improved memory compared with CTRL group. Furthermore, both CT and PT have an impact on selective attention, shifting ability and executive functions.

The effects of CT on mental flexibility, memory, executive function, processing speed, attention, and fluid intelligence was demonstrated in a previous RCT [25] and systematic review [33].

Exercise to prevent dementia and delay cognitive decline have gained considerable attention in recent years [34]. In particular, several studies have demonstrated that PT can impact attention [25, 35, 36]