

Vascular Function Is Improved After an Environmental Enrichment Program The Train the Brain–Mind the Vessel Study

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Abstract—Environmental enrichment may slow cognitive decay possibly acting through an improvement in vascular function. Aim of the study was to assess the effects of a 7-month cognitive, social, and physical training program on cognitive and vascular function in patients with mild cognitive impairment. In a single-center, randomized, parallel-group study, 113 patients (age, 65–89 years) were randomized to multidomain training (n=55) or usual care (n=58). All participants underwent neuropsychological tests and vascular evaluation, including brachial artery flow-mediated dilation, carotid–femoral pulse wave velocity, carotid distensibility, and assessment of circulating hematopoietic CD34+ and endothelial progenitor cells. At study entry, an age-matched control group (n=45) was also studied. Compared with controls, patients had at study entry a reduced flow-mediated dilation ($2.97\pm 2.14\%$ versus $3.73\pm 2.06\%$; $P=0.03$) and hyperemic stimulus (shear rate area under the curve, 19.1 ± 15.7 versus $25.7\pm 15.1\times 10^{-3}$; $P=0.009$); only the latter remained significant after adjustment for confounders ($P=0.03$). Training improved Alzheimer disease assessment scale cognitive (training, 14.0 ± 4.8 to 13.1 ± 5.5 ; nontraining, 12.1 ± 3.9 to 13.2 ± 4.8 ; P for interaction visit \times training=0.02), flow-mediated dilation ($2.82\pm 2.19\%$ to $3.40\pm 1.81\%$, $3.05\pm 2.08\%$ to $2.24\pm 1.59\%$; $P=0.006$; $P=0.023$ after adjustment for diameter and shear rate area under the curve), and circulating hematopoietic CD34+ cells and prevented the decline in carotid distensibility (18.4 ± 5.3 to 20.0 ± 6.6 , 23.9 ± 11.0 to 19.5 ± 7.1 Pa $^{-1}$; $P=0.005$). The only clinical predictor of improvement of cognitive function after training was established hypertension. There was no correlation between changes in measures of cognitive and vascular function. In conclusion, a multidomain training program slows cognitive decline, especially in hypertensive individuals. This effect is accompanied by improved systemic endothelial function, mobilization of progenitor CD34+ cells, and preserved carotid distensibility.

Clinical Trial Registration—URL: <http://www.clinicaltrials.gov>. Unique identifier: NCT01725178.

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Key Words: cognitive dysfunction ■ control groups ■ endothelial progenitor cells ■ humans ■ vascular stiffness

The traditional classification of dementia distinguished vascular cognitive impairment from Alzheimer disease, describing different pathophysiological pathways. More recently, it has been hypothesized that even Alzheimer disease can be viewed as a predominantly vascular disorder.^{1,2} Indeed, it shares with cardiovascular disease several risk factors, as well as some mechanisms of disease, including the NO pathway.^{3,4} Furthermore, structural alterations that are an expression of vascular aging, such as a large artery stiffness⁵⁻⁷ and carotid atherosclerosis,^{8,9} have been associated with a steeper cognitive decline.

Based on these findings, it is conceivable that interventions aimed at restoring endothelial function and reducing large artery stiffness might be beneficial in prevention of dementia. In the past few years, there has been a growing interest toward multidomain interventions for prevention of dementia, including lifestyle measures, cognitive training, and vascular risk monitoring, especially in individuals at increased risk,¹⁰ but to date, few and conflicting data exist about the effect of multidomain interventions on vascular biomarkers and their possible role in dementia prevention. Thus, the diagnostic and therapeutic implications of the acknowledgment of vascular roots of dementia remain elusive.²

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*A list of all the Train the Brain Consortium members is given in the Appendix.

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Within this framework, the Italian National Research Council launched a prospective, randomized, parallel-group, open-label clinical trial called Train the Brain, enrolling elder patients with mild cognitive impairment (MCI), to investigate the efficacy of a protocol of physical exercise and cognitive stimulation on cognitive and vascular function. MCI is a sub-clinical condition favoring the clinical onset of dementia¹¹ and is possibly associated with impaired vascular function.¹²

Whereas the results regarding the primary outcome (cognitive function) were published elsewhere,¹³ the analysis presented in this article is aimed at investigating the relationship between vascular function and structure and cognitive function (the Train the Brain–Mind the Vessel study). Specifically, the 2 main objectives were

- to identify, in a cross-sectional analysis, vascular features associated with MCI in comparison with controls with normal cognitive function;
- to investigate, in an interventional prospective study, the effects of a program of environmental enrichment, including cognitive, social, and exercise training, on vascular function and structure and the possible relationship between cognitive and vascular outcomes.

Methods

Study Protocol

An expanded Methods section, including a detailed description of the multimodality training program and measurements, is available in Methods in the [online-only Data Supplement](#) and Figure S1 in the [online-only Data Supplement](#). The data that support the findings of this study are available from the corresponding author on reasonable request.

Results

Cross-Sectional Study: Comparison Between MCI and Non-MCI

One hundred fifty-eight patients in total were recruited for the Train the Brain study; 113 subjects were defined as having MCI at the neurological examination; 45 were not. Among them, 131 participants accepted to undergo the cardiovascular evaluation at baseline, 91 MCI and 40 non-MCI (Figure 1).

Baseline clinical characteristics are shown in Table S1. The 2 groups showed no significant differences in the main clinical characteristics, with the exception of age. As expected, ADAS-cog was lower in patients with non-MCI than in MCI (8.9 ± 3.3 versus 13.6 ± 4.6 ; $P=0.004$).

Flow-mediated dilation (FMD) assessment was successful in 36 non-MCI (90%) and in 85 MCI (93%). Main reasons for failure were arm movements during the examination and low-quality images. MCI showed a reduced FMD and hyperemic stimulus (evaluated as peak hyperemic shear rate [SR] and SR area under the curve [AUC] until peak time) in comparison with non-MCI, whereas brachial artery diameter and response to glyceryl trinitrate were similar (Table 1). FMD was no longer significantly different between MCI and non-MCI when SR AUC was added as a covariate ($P=0.18$). When results were adjusted for age, body mass index, and total cholesterol, only the difference in SR AUC remained statistically significant ($P=0.03$), whereas the difference in FMD and peak hyperemic SR was attenuated ($P=0.19$ and 0.14 , respectively). No differences were found in

carotid–femoral pulse wave velocity (PWV), aortic pressure or its augmentation, and carotid geometry or elasticity (Table 1).

The number of circulating progenitor cells was measured in 36 non-MCI (90%) and 68 MCI (75%). MCI and non-MCI showed similar number of CD34⁺ (1.3 ± 0.8 versus 1.7 ± 1.4 n/μL; $P=0.14$) and endothelial progenitor cells (EPC; 0.05 ± 0.08 versus 0.04 ± 0.05 n/μL; $P=0.78$).

Effect of Training on Clinical and Cognitive Characteristics

Clinical characteristics of MCI individuals accepting to perform vascular evaluation and completing the 7-month follow-up were reported in Table S2. There were no differences at baseline in clinical characteristics, except for a higher prevalence of statin use in MCI nontraining individuals, with similar cholesterol values (Table S2). Furthermore, no differences in main clinical characteristics were found in MCI individuals accepting to enter the vascular substudy as compared with those enrolled in the main study.¹³

ADAS-Cog (Alzheimer Disease Assessment Scale Cognitive), which was significantly different at T0 ($P<0.05$), increased after the 7-month period, in the nontraining and decreased in the training group, with statistical significance for both the time/treatment interaction and the intragroup comparisons, thus showing a positive effect of the intervention (14.0 ± 4.5 to 13.1 ± 5.5 for MCI training; 12.1 ± 3.9 to 13.2 ± 4.8 for MCI nontraining; $\text{time}\times\text{treatment } P=0.02$).

Office blood pressure (BP) was similarly and significantly reduced in MCI training ($141.3\pm 15.8/72.9\pm 7.9$ to $133.8\pm 14.6/68.6\pm 8.7$ mm Hg) and MCI nontraining ($141.3\pm 18.8/72.7\pm 10.4$ to $136.1\pm 15.3/68.2\pm 9.0$ mm Hg). However, an increase in number of antihypertensive drugs or in dosage $\geq 50\%$ occurred in a significantly greater proportion of MCI nontraining ($n=6$, 18.8%) versus MCI training ($n=1$, 1.9%; $P=0.006$). No significant changes in body mass index, heart rate, lipid, and glucose profile were found (Table S3).

Effect of Training on Vascular Variables

When vascular characteristics at T0 were compared between the 2 treatment arms, MCI nontraining showed a higher hyperemic stimulus for FMD, both expressed as peak hyperemic SR and SR AUC, than MCI training (Table 2). The 2 treatment arms had different SR AUC at baseline, which, however, did not change after 7 months in any group. Brachial artery diameter showed also a significantly different behavior over time in the 2 groups, indicating a more favorable remodeling in MCI training (Table 2; Figure 2). FMD in the brachial artery had a diverging trend over time in the 2 treatment arms. In particular, FMD showed an increase in the training arm and a reduction in the control arm ($\text{time}\times\text{treatment } P=0.006$). In the mixed-model analysis, a significant interaction $\text{visit}\times\text{training}$ ($P=0.017$) was confirmed even when considering brachial artery diameter and SR AUC as covariates; furthermore, FMD at T7 was higher in the training than in the nontraining group ($P=0.016$, Bonferroni post hoc comparison test). Response to glyceryl trinitrate was similar in the 2 treatment arms and unchanged from T0 to T7.

Comparing vascular characteristics at T0, MCI nontraining showed a higher carotid distension, leading to a significantly higher distensibility and stiffness and lower PWV than

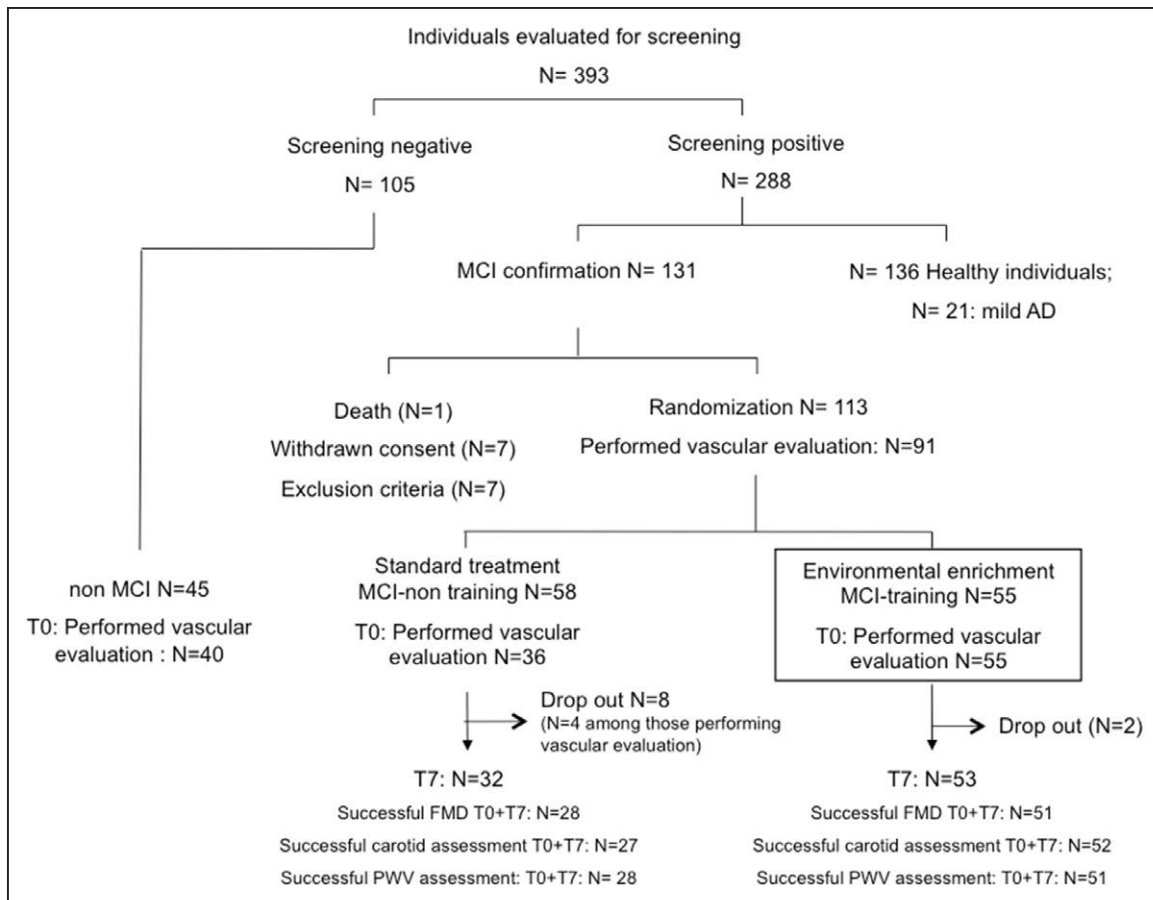


Figure 1. Flowchart of the study. AD indicates Alzheimer disease; FMD, flow-mediated dilation; MCI, mild cognitive impairment; and PWV, pulse-wave velocity.

MCI training (Table 2). A diverging trend between groups was observed for carotid distensibility. Indeed, distensibility, which was higher at T0 in MCI nontraining than in MCI training group, was reduced over time in the MCI nontraining and preserved in MCI training, with a significant interaction time–treatment (Figure 2). The other carotid parameters had a similar behavior: in particular, elastic modulus was increased from T0 to T7 in the control but not in the treatment arm (Table 2). In parallel with the brachial artery, exercise and cognitive training tended to prevent negative carotid remodeling, whereas no significant effect was observed on intima–media thickness (Figure 2). There was no difference in the behavior over time of carotid–femoral PWV, central BP, and its augmentation, which were unchanged in both groups.

After 7 months of training, a significant increase in CD34⁺ cells (1.17 ± 0.7 to 1.53 ± 0.6 per μL ; $P=0.004$), but not in EPC (0.06 ± 0.08 to 0.05 ± 0.08 per μL ; $P=0.26$), was only observed in MCI training group, suggesting a favorable effect of the training on the hematopoietic cell mobilization. No significant changes in either CD34⁺ cells (1.8 ± 0.9 versus 1.4 ± 0.3 per μL ; $P=0.16$) or EPC (0.05 ± 0.07 versus 0.039 ± 0.06 per μL ; $P=0.77$) were found in MCI nontraining.

Predictors of Cognitive Outcome in MCI Training

In the MCI training group, established hypertension at study entry was the only clinical variable associated with a

significantly greater improvement of ADAS-cog after training ($\Delta\text{ADAS-cog}$, -2.3 ± 2.7 in hypertensive versus 0.3 ± 5.0 in normotensive patients; $P=0.02$). In particular, no differences between sexes were found ($\Delta\text{ADAS-cog}$, -1.2 ± 4.6 in women versus -0.7 ± 3.8 in men; $P=0.52$), whereas no significant correlation between age at T0 and $\Delta\text{ADAS-cog}$ was found ($r=0.006$; $P=0.94$). Indeed, a significant reduction in ADAS-cog was observed only in hypertensive patients, with a significant time \times group interaction (Figure 3). Furthermore, absolute ADAS-cog change was significantly and inversely correlated to aortic systolic BP at T0 ($r=-0.32$; $P=0.02$; Figure S2), PP at T0 ($r=-0.35$; $P=0.01$), and number of anti-hypertensive drugs at T0 ($r=-0.30$; $P=0.03$). Interestingly, this result occurred regardless of the degree of mean BP reduction, which was similar in hypertensive and normotensive individuals (Figure 3). Among vascular characteristics at T0, hyperemic SR AUC ($r=0.37$; $P=0.009$), carotid stiffness ($r=-0.32$; $P=0.02$), and Young elastic modulus ($r=-0.37$; $P=0.009$) were significantly associated with $\Delta\text{ADAS-cog}$ in the univariate analysis. However, all these associations lost significance when adjusted for hypertensive status ($P=0.29$, 0.14 , and 0.18 , respectively). Finally, $\Delta\text{ADAS-cog}$ was not associated with absolute changes in either mean BP ($r=0.01$; $P=0.93$) or any of the vascular parameters measured, neither in the whole MCI training group, nor in the hypertensive/normotensive individuals (data not shown).

Table 1. Vascular Variables at T0 (Non-MCI vs MCI)

Variables	Non-MCI	MCI	P Value
	n=39	n=83	
Mean carotid diameter, mm	7.86±0.83	8.00±0.87	0.45
Diastolic carotid diameter, mm	7.60±0.82	7.76±0.84	0.34
Intima–media thickness, μ m	754±131	773±158	0.92
Distension, mm	0.515±0.125	0.543±0.154	0.42
Compliance, mm ² KPa ⁻¹	0.87±0.25	0.93±0.34	0.45
Distensibility, Pa ⁻¹	19.5±6.3	20.0±7.9	0.73
Stiffness, m/s	7.49±1.09	7.52±1.19	0.96
Elastic modulus, KPa	505.5±181.6	521.5±232.7	0.94
Carotid PP, mm Hg	56.2±12.3	59.5±16.5	0.48
	n=38	n=89	
Augmentation pressure, mm Hg	18.1±6.0	17.9±7.6	0.85
Augmentation index, %	34.3±9.7	30.7±8.7	0.053
Aortic systolic BP, mm Hg	128.0±14.0	127.0±15.8	0.74
Aortic PP, mm Hg	53.0±11.2	55.3±14.0	0.38
Mean BP, mm Hg	96.8±10.1	94.1±10.2	0.18
HR, bpm	63.9±8.2	65.3±11.0	0.48
Pulse wave velocity, m/s	10.47±1.94	10.86±2.00	0.34
	n=35	n=86	
Baseline brachial artery diameter, mm	4.14±0.79	4.30±0.86	0.25
FMD, %	3.69±2.07	3.00±2.14	0.03
Baseline shear rate, s ⁻¹	321±123	305±170	0.20
Peak hyperemic shear rate, s ⁻¹	1329±754	1066±640	0.06
SR AUC, s ⁻² ×10 ³	25.7±15.0	19.2±15.7	0.009
Dilation to nitroglycerin, %	7.65±4.52	6.37±3.50	0.11

AUC indicates area under the curve; BP, blood pressure; FMD, flow-mediated dilation; HR, heart rate; MCI, mild cognitive impairment; PP, pulse pressure; and SR, shear rate.

Discussion

The Train the Brain study, was a prospective, randomized, parallel-group, open-label clinical trial conducted by Italian National Research Council (CNR) aimed at investigating the safety and efficacy of a multimodality training program on vascular and cognitive outcomes in individuals at risk for developing dementia.

The main finding of the Train the Brain–Mind the Vessel study is that in MCI, a 7-month multidomain training program is able to induce a significant improvement in vascular end points, such as systemic endothelial function and carotid distensibility, and to slow cognitive decline, though modestly. The proposed training opposes the physiological effect of aging on arterial vessels, namely endothelial dysfunction, negative arterial remodeling, and loss of elasticity. An original finding is that the multidomain training program is more effective in hypertensive rather than in normotensive MCI individuals, indicating that an intervention aimed at combating the vascular roots of dementia is more beneficial in this subset of population, in whom this mechanism is probably more relevant.

Effects of Training on Endothelial Function

A combined 7-month cognitive and exercise training is able to increase FMD and CD34⁺ cell mobilization in patients with MCI. Based on these results it is possible to speculate that endothelial dysfunction might be a crucial mechanism of disease and a reasonable target for prevention of dementia, though the study design does not allow to demonstrate that the training-induced improvement in cognitive function and in vascular function is causally related. CD34⁺ cells are a more immature population of bone marrow-derived progenitors, including EPCs and nonendothelial progenitor cells, which potentially involved in maintenance of the vascular homeostasis.¹⁴ Mobilization of progenitor pluripotent cells from the bone marrow, activated by the multidomain training, might contribute to the restoration of vascular integrity and functionality.¹⁴ NO plays a critical role in the mobilization of progenitor cells¹⁵ and in the FMD response.¹⁶ Experimental studies demonstrated that reduced brain NO availability causes increased β -amyloid deposition by several mechanisms, including hypoperfusion and altered β -amyloid clearance,^{3,4} suggesting that loss of cerebral endothelial NO plays a role in the initiation and progression of cognitive decline.⁴ Conversely, conflicting data exist in humans: 2 small case–control studies indicate that either FMD¹² or the reactivity of skin microcirculation¹⁷ is altered in initial cognitive impairment, whereas in the general population of the Framingham Offspring Study, FMD is not associated with brain volume or cognitive function tests.¹⁸ However, it is important to acknowledge that impaired FMD in MCI is at least, in part, mediated by concomitant classical cardiovascular risk factors, as indicated by the attenuation of the difference between MCI and healthy controls when adjusted for confounders, as well by reduced hyperemic stimulus, which is per se an index of microvascular dysfunction. This is in line with our results on progenitor cells, showing no significant differences in CD34⁺ and EPC levels between patients with MCI and healthy individuals, as reported also in a previous study.¹⁹ On the other hand, epidemiological evidence suggests that several traditional CV risk factors, all associated with reduced endothelial NO availability,²⁰ predispose to dementia^{2,21} and that their treatment might prevent it¹⁰. Further studies are needed to demonstrate whether endothelial dysfunction is the missing link between exposure to cardiovascular risk factors and dementia.

Though the presence of endothelial dysfunction in patients with MCI cannot be clearly demonstrated in our study, the relevant effect of multimodality training on 2 different measures of systemic endothelial function suggests that progression to dementia might be slowed through endothelium-related mechanisms.

Effects of Training on Large Artery Distensibility

It is well established that increased carotid–femoral PWV—a key marker of vascular aging—is associated with cognitive decline.^{3,5,6,21} In contrast, neutral results were found in the Rotterdam Study for carotid stiffness.⁷ In the Train the Brain–Mind the Vessel study, a comprehensive vascular characterization was performed at 2 distinct time points, demonstrating the effectiveness of a rather short-term and low-intensity intervention on cognitive and vascular outcomes in elderly individuals at risk for dementia. Reduced carotid distensibility might directly

Table 2. Behavior of Vascular Variables at T0 and T7 in Patients With MCI Randomized to Active Treatment (MCI Training) or Usual Care (MCI Nontraining)

Variables	MCI Nontraining		MCI Training		P Value
	n=28		n=51		
Dilation to nitroglycerin, %	6.80±3.14	7.01±4.28	6.24±3.70	6.84±3.72	0.72
Baseline shear rate, s ⁻¹	291±113	249±111	317±199	308±246	0.48
Peak hyperemic shear rate, s ⁻¹	857±423	722±303	1205±728*	1022±664	0.78
	n=27		n=52		
Diastolic carotid diameter, mm	7.66±0.97	7.73±0.88	7.83±0.75	7.61±0.83	0.07
Wall cross-sectional area, mm ²	16.9±5.2	17.3±5.3	17.1±3.5	16.2±3.5	0.21
Distension, mm	0.619±0.180	0.517±0.140†	0.512±0.130*	0.516±0.160	0.01
Compliance, mm ² KPa ⁻¹	1.07±0.46	0.88±0.26	0.87±0.25*	0.89±0.31	0.03
Stiffness, m/s	7.02±1.42	7.57±1.37	7.72±1.03*	7.46±1.07	0.02
Elastic modulus, KPa	444.5±182.3	512.8±215.8†	557.4±253.7*	491.6±148.1	0.03
Carotid PP, mm Hg	60.6±18.6	56.5±14.4	57.7±13.7	54.6±11.9	0.77
	n=28		n=51		
Augmentation pressure, mm Hg	16.2±6.4	18.7±10.3	17.5±6.9	17.6±8.3	0.19
Augmentation index, %	29.1±8.7	30.3±9.1	31.3±8.4	30.7±10.8	0.39
Aortic systolic BP, mm Hg	125.8±13.0	130.3±20.7	126.2±14.8	126.9±16.2	0.38
Aortic PP, mm Hg	54.3±13.6	58.0±18.3	54.4±11.8	54.6±12.9	0.27
Mean BP, mm Hg	93.2±9.7	95.6±13.4	94.1±9.9	94.7±11.9	0.57
HR, bpm	67.5±9.8	65.3±11.1	65.0±11.6	66.3±11.1	0.09
Pulse wave velocity, m/s	10.22±1.43	10.47±1.48	11.09±2.23*	11.22±2.36*	0.66

P value is for interaction time–treatment (repeated measures ANOVA). BP indicates blood pressure; HR, heart rate; MCI, mild cognitive impairment; and PP, pulse pressure.

* $P < 0.05$ vs MCI nontraining (Tukey–Kramer post hoc multiple comparison test).

† $P < 0.05$ vs T0.

cause increased transmission of pressure and flow pulsatility to the microcirculation, as well as plaque rupture and embolization, thus causing brain hypoperfusion, which is a trigger for β -amyloid deposition.^{2,22} Given the known BP dependence of vascular stiffness parameters, it is of relevance that the beneficial effect on carotid elasticity in the treatment group was achieved in the presence of a BP reduction similar to the control group and with a substantially stable glucose and lipid profile in both groups. These results are also supported by the significant effect of training not only on distensibility but also on Young elastic modulus—an index of the intrinsic stiffness of wall material. In our view, lack of effect of training on carotid–femoral PWV is not in contrast with its well-known association with cognitive decline in large population studies but is rather because of its unresponsiveness to physical exercise; indeed, a recent review of the current literature pointed out that PWV is hardly modifiable by exercise in middle-aged and older adults with hypertension.²³

Hypertension as a Predictor of Cognitive Outcome in MCI

Hypertension is considered a major risk factor for cognitive decline and dementia.²⁴ Experimental studies suggest that hypertension induced by transverse aortic coarctation is able to induce brain β -amyloid deposition and cognitive impairment acting on vascular mechanisms.²⁵ In humans, pooled analysis

of several randomized controlled trials testing BP-lowering drugs in the elderly showed that BP reduction is associated with a reduced incidence of dementia, even after a follow-up of few years.^{26,27} It is also conceivable the reduced incidence of dementia during the last 3 decades is attributable, at least in part, to a better treatment of vascular risk factors, including hypertension.²⁸ In our study, the only predictor of cognitive response to the combined physical and cognitive training is a previous diagnosis of hypertension. Of note, the improvement in cognitive function after training is not related to BP reduction achieved in this relatively short-term intervention trial. It is conceivable that vascular alterations play a role in development of cognitive impairment only in individuals with established cardiovascular risk factors, such as hypertension. Within the spectrum ranging from Alzheimer disease to vascular cognitive impairment, pathogenesis of dementia in normotensive individuals might be more tightly related to extravascular factors, making negligible the positive impact of physical training.

Limitations

A major limitation of the study is that in the MCI nontraining group, the acceptance rate to the vascular substudy was only 62%, and the dropout rate during the intervention, though low in both groups, was higher compared with that in MCI training, leading to an underrepresentation of the control arm, with

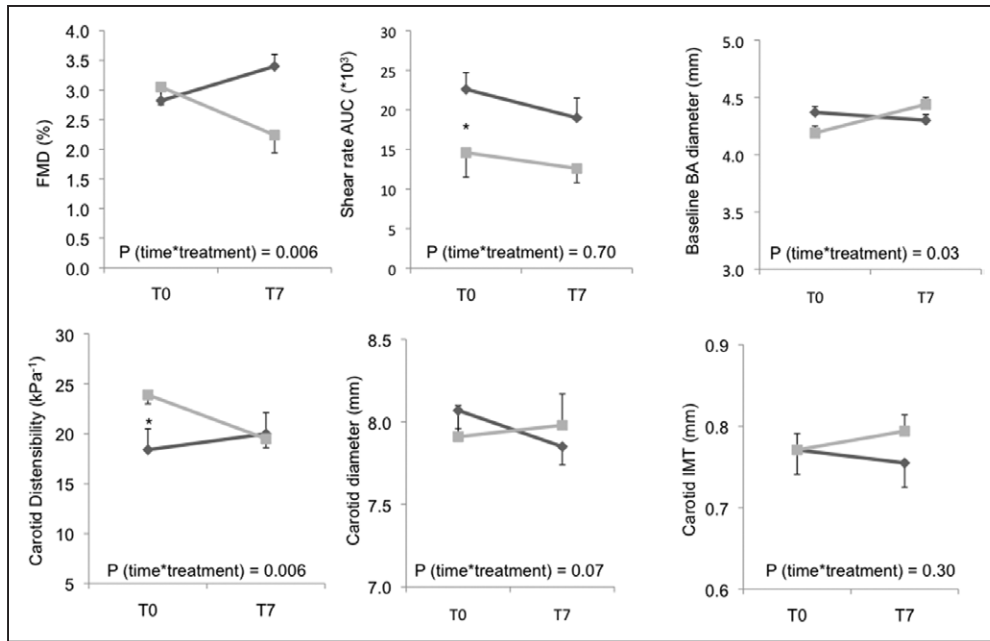


Figure 2. Behavior of main vascular parameters in mild cognitive impairment (MCI) individuals at T0 and T7. Data are expressed as mean±SEM. *P* values (time×treatment) were obtained by repeated measures ANOVA. AUC indicates area under the curve; BA, brachial artery; FMD, flow-mediated dilation; and IMT, intima–media thickness. **P*<0.05, MCI training (dark gray) vs MCI nontraining (light gray) in post hoc analysis.

possible introduction of a selection bias. Furthermore, though the 2 treatment arms were matched for the main clinical characteristics, the MCI training group had a higher ADAS-cog and a lower carotid distensibility at baseline: this fact might have influenced the results of the study because of regression to the mean.

The implementation of a multidomain training, though coherent with the multifactorial pathophysiology of dementia and supported by current literature,^{10,29,30} did not allow identifying which training component is the most effective on vascular variables and cognitive function. It is conceivable that most of the beneficial effects on the vasculature are related to exercise training,³¹ which is able to improve NO availability³² and has a sympathoinhibitory effect.³³ On the contrary, though interventions aimed at restoring vascular health might

contribute to reduce the global burden of dementia,³⁰ we cannot completely exclude that improvement of cognitive function in our study was induced mainly by the cognitive training only. Furthermore, it is important to acknowledge that another important component of the study intervention is to counteract social isolation—an established risk factor and therapeutic target for dementia³⁴—is now considered an emerging cardiovascular risk factor, increasing per se cardiovascular morbidity and mortality.³⁵ The design of the study does not allow demonstrating that the training-induced improvements in cognitive function and vascular function are causally related. In the present study, endothelial dysfunction was measured in the brachial artery, whereas NO-related mechanisms favoring dementia were demonstrated in the cerebral circulation and in experimental settings. These results are hardly translatable to humans because currently available noninvasive techniques^{36,37} may not measure accurately the cerebral endothelial function. Finally, because the T7 visit occurred 7 to 21 days after the end of the intervention, the observed improvements in vascular function may have been underestimated.

Perspectives

In conclusion, a nonpharmacological, combined physical, social, and cognitive training slows, and partly reverses, the decline in cognitive function, endothelial function, and carotid elasticity in a population of elderly individuals with MCI. The results of the present study suggest a role of vascular factors in the individuals. Accordingly, the proposed intervention to prevent cognitive decline might find its clinical application in the hypertensive subset of population at risk of dementia. However, this hypothesis should be taken with caution because there seems to be no correlation between changes in vascular and cognitive function at the individual level and need to be

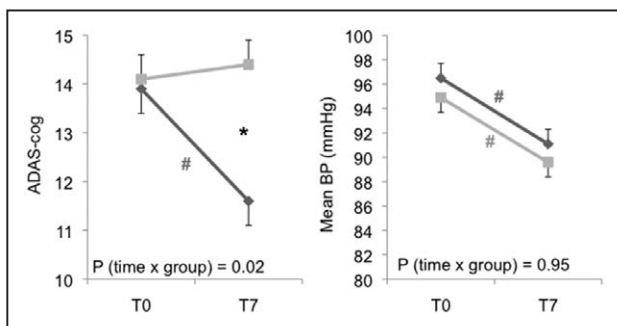


Figure 3. Effect of multidomain training of ADAS-cog and mean blood pressure (BP) in hypertensive and normotensive groups in the mild cognitive impairment (MCI) training treatment arm. Data are expressed as mean±SEM. *P* values (time×group) were obtained by repeated measures ANOVA. Yellow squares: hypertensive MCI-training patients; green squares: normotensive MCI-training patients. **P*<0.05, hypertensive vs normotensive MCI training patients in post hoc analysis; #*P*<0.05 T0 vs T7 in post hoc analysis.

supported by larger prospective studies aimed at investigating whether interventions aimed at improving vessel structure and function will translate in slowing cognitive decline.

Appendix

Train the Brain Consortium Members

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Disclosures

None.

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Novelty and Significance

What Is New?

- In individuals with mild cognitive impairment, who are at risk for dementia, a 7-month cognitive and physical training program had a positive effect on cognitive function.
- The training program increases endothelial function, circulating hematopoietic CD34+ cells and reduced carotid stiffness.

What Is Relevant?

- Cognitive function was improved by the combined training program only in hypertensive individuals.

Summary

A 7-month multidomain training slows, though modestly, cognitive decline, especially in hypertensive individuals. This effect is accompanied by improved systemic endothelial function and preserved carotid distensibility.