Research report

Cognitive gains and cortical thickness changes after 12 weeks of resistance training in older adults with low and high risk of mild cognitive impairment: Findings from a randomized controlled trial

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ABSTRACT

Background: In this randomized controlled trial, we assessed the neuroprotective effect of a 12-week resistance training (RT) program on executive control and cortical thickness of the prefrontal, temporal, parietal, and central cortex, regions prone to structural decline in individuals with mild cognitive impairment (MCI).
Methods: Seventy older adults (aged 60–85 y old, 38 females and 32 males) were randomly allocated to a 12-week lower limb RT program or a waiting list control group. The Montreal Cognitive Assessment (MoCA) was used to stratify participants screened for high (< 26) or low (≥ 26) MCI risk. Cognitive measurements consisted of the two-choice reaction time, Go/No-go, mathematical processing, and memory search tests. Cortical thickness was estimated from 3D T1-weighted MR images.
Results: Complete randomized controlled trial data was obtained from 50 individuals (24 with high MCI risk). Significant Group x Time interactions were found for response on the Go/No-go task and cortical thickness of the right parahippocampal gyrus [$F \geq 5.3$, $p \leq 0.03$; $\eta_p^2 \geq 0.12$]. An inspection of these observations revealed an increase in cortical thickness ($+1.18$ %) and a decrease in response time (-4.35 %) in individuals with high MCI risk allocated to the exercise group (both uncorrected $p = 0.08$). Decreased response time on the Go/No-go task was associated with increased cortical thickness in the right entorhinal gyrus (uncorrected $p = 0.01$).
Conclusions: Our study demonstrated that 12 weeks of RT intervention may effectively improve cognitive performance and slow neuronal loss in the hippocampal complex of older adults at high MCI risk. Findings support evidence for the neuroprotective effects of resistance training and its potential role in cognitive health.

1. Introduction

Normal aging is characterized by declines in the integrity and functioning of the central nervous system, leading to a reduction in cognitive and motor abilities that may vary in severity among individuals (Gonzales et al., 2022; Liang and Carlson, 2020; Nyberg et al., 2020). Some cognitive declines (such as memory loss) are associated with accelerated neurodegenerative processes and can become apparent

before the onset of dementia-related symptoms, indicating a pre-clinical stage known as mild cognitive impairment (MCI) (Cloutier et al., 2015; Grundman et al.; Dickerson et al., 2007). Furthermore, MRI studies have shown that atrophy of frontal and temporal regions, including the hippocampus, can begin several years before cognitive impairment (Flak et al., 2018; Wei et al., 2021) and correlate with the degree of cognitive impairment at the time of MCI diagnosis (Devivo et al., 2019; Nurdal et al., 2020). However, medial temporal lobe atrophy and hippocampal volumetric loss are not specific to MCI (Lombardi et al., 2018) and the mechanisms leading to a transition from normal cognitive aging to MCI are still unclear. For example, Alzheimer-like lesions that are mostly seen in the frontal, temporal, and parietal cortices may occur sub-clinically in older adults with normal cognitive function without the manifestation of clinical symptoms (Bjorkli et al., 2020; Krance et al., 2019). More specifically, executive functions (Chehrehnegar et al., 2022), including inhibitory control, set-shifting, and working memory (Eriksson et al., 2015; Kim et al., 2016), tend to deteriorate earlier than memory (Kirova et al., 2015; Quentin and Cohen, 2019) and general cognitive decline (Kim et al., 2016; Si et al., 2020).

The loss of executive functions, such as planning, switching/set-shifting, working memory, and inhibitory control correlate with declining functional abilities, affecting quality of life (Verreckt et al., 2022), social and psychological well-being (Tomaszewski Farias et al., 2009). However, a growing body of evidence supports the importance of physical activity as a non-pharmacological intervention for mitigating cognitive declines in older adults with MCI (Bisbe et al., 2020; Zhang et al., 2023a). For example, long-term studies show that older adults with active lifestyles maintain better cognitive function compared to their sedentary peers (Dieckelmann et al., 2023; Huang et al., 2022). Furthermore, evidence from individual randomized controlled trials (RCTs) and meta analyses suggests that physical exercise interventions can improve brain structural and functional integrity (Chirles et al., 2017; Suzuki et al., 2013; Teixeira et al., 2018; Colcombe and Kramer, 2003; Demurtas et al., 2020; Zhang et al., 2020; Coelho-Júnior et al., 2020; Kim et al., 2022; Liu-Ambrose et al.,; Sheoran et al., 2023; Tao et al., 2019; Vints et al., 2024a, 2024c); and reduce the prevalence of dementia-related diseases, especially among individuals with a high genetic risk (de Frutos Lucas et al., 2023; de Frutos-Lucas et al., 2020; Gronek et al., 2019).

To explain the mechanisms at play, chronic exercise interventions have been shown to reduce inflammatory markers while boosting neurotrophic factors, leading to a neuroprotective effect (Fang et al., 2022). These benefits have been observed across various types and intensities of exercise (Ahlskog et al., 2011), although the majority of research has focused on endurance exercise more than on resistance training (Huang et al., 2022; Aghjayan et al., 2022). Evidence suggests, nevertheless, that resistance training may cause larger release of neurotrophic and anti-inflammatory factors into the bloodstream (Tsai et al., 2019; Ostrowski et al., 2016; Carro et al., 2000; Ding et al., 2006; Vaynman et al., 2004; Griseta et al., 2023). The interrelationship between resistance training, blood biomarkers, hippocampal neurometabolites, hippocampal subfield volumes, and cognitive functioning has been recently explored by our group (Sheoran et al., 2023; Vints et al., 2024a,c). Taken together, findings from these studies revealed multifactorial effects of resistance training on physiological and cognitive function, particularly in older adults with high MCI risk. For example, it was found that exercise-induced changes in neurochemical and structural properties of the hippocampus were more pronounced in older adults with some cognitive impairment than in cognitively intact older adults (Vints et al., 2024c). Furthermore, observations revealed an inverse relationship between high expression of the inflammatory neurometabolic marker N-acetyl-aspartate to myoinositol ratio and the hippocampal CA1 subfield volume (Vints et al., 2024c) in the exercise group, suggesting that exercise-induced decrease in neuroinflammation and exercise-induced gains in hippocampus volume were interrelated. Such a trend was also noted in the association between performance gains and

exercise-induced changes in the expression of growth factors, illustrated by the finding that larger increases in IGF-1 levels following resistance training were associated with larger improvements in response time on a mathematical processing task (Vints et al., 2024a). Finally, our previous findings (Vints et al., 2024a) showed that resistance training enhanced the improvement over time on an inhibition task to a greater extent in older adults with high MCI risk compared to healthy older adults.

The primary aim of the current study was to complement those previous findings by investigating the neuroprotective effect of a 12-week resistance training program on brain cortical thickness, a biomarker of gray matter integrity. If such changes are observed, it will support an indirect link between (1) exercise-induced changes in brain structure and (2) exercise-induced changes in the expression of neurometabolites and/or blood biomarkers that have been reported in our previous work (Sheoran et al., 2023; Vints et al., 2024a,c). Our secondary aim was to examine if structural changes materialized in cognitive performance changes. Based on findings from previous reviews and behavioral studies on aging (Cleeland et al., 2019; Michely et al., 2018; Nelson et al., 2022; Tsapanou et al., 2019; Voss et al., 2013; Zhao et al., 2021) we focused specifically on substructures of the prefrontal cortex (PFC) and the medial-temporal lobe surrounding the hippocampus that are known to be affected in MCI and Alzheimer's disease. These include: (1) the rostral mediofrontal area of the frontal lobe, which plays a crucial role in attentional reorientation, working memory, speech, and language comprehension (Briggs et al., 2021); (2) the superiofrontal gyrus, which is thought to contribute to higher cognitive functions, in particular, working memory (Nissim et al., 2017; Hone-Blanchet et al., 2022; Tisserand et al., 2002) and episodic memory (inferotemporal and parahippocampal cortex); (3) the entorhinal and parahippocampal areas, which are crucial in mediating signaling between the hippocampus and the prefrontal cortex (Sexton et al., 2016), and (4) the inferioparietal cortex, which is essential for mathematical operations and is involved in language (Wei et al., 2021). In line with our previous observations (Vints et al., 2024a,c), we expected that the beneficial effects of resistance training on both structure and function would be more pronounced in older adults at high risk of MCI compared to low-risk adults.

2. Methods

2.1. Participants and setting

Seventy older adults (38 females, 32 males) aged 60–85 years were recruited for this RCT between July 2020 and July 2021. The same cohort was also included in previous studies (Sheoran et al., 2023; Vints et al., 2024a,c). The study methods were approved by the Kaunas Regional Biomedical Research Ethics Committee (No. BE-10-7). A written informed consent was obtained from all participants before their inclusion in the study. Participants were recruited via presentations in local community organizations and personal contacts with the experimenters (co-authors S.K., V.J.C., and N.M). Participants were not included if they participated in an exercise program regularly in the last six months. Further exclusion criteria were alcohol or drug abuse, neurologic, oncologic or psychiatric diagnosis, use of psychopharmacological drugs in the last five years, a history of chemotherapy, or signs or symptoms of cardiovascular, pulmonary or metabolic diseases. Participants had to be physically healthy and able to perform ten sit-ups. They had to be allowed to undergo MRI scanning according to the checklist provided by the Department of Radiology at the Lithuanian University of Health Science. Participants were allowed to withdraw from the study at any time. All participants underwent the Montreal Cognitive Assessment (MoCA) test and psychological health assessment tests conducted in a clinical environment by a qualified mental healthcare specialist (coauthor S.K) before being included in the study. None of the participants was diagnosed with dementia, and all of them scored 19 or above on the MoCA test. Participants were asked to complete a

demographics questionnaire assessing their age, sex, educational level (primary education, secondary education, or higher education), and smoking status. Self-reported physical activity level was estimated using the International Physical Activity Questionnaire – Short Form (IPAQ-SF) (Sjostrom et al., 2005; Hagstromer et al., 2010).

2.2. Study design

The study design included a two-group randomized controlled trial with 12 weeks of resistance training intervention and a passive control group. This design was previously described (Sheoran et al., 2023; Vints et al., 2024a,c) and is illustrated in Fig. 1. The randomization protocol included a stratified permuted block procedure (Vints et al., 2024a) with the participants' scores on the Montreal Cognitive Assessment (MoCA) test as a stratification factor. Participants were subdivided into MCI low risk (MoCA scores $\geq$ 26) and MCI high risk (MoCA scores $\leq$ 25) subgroups (Nasreddine et al.,). In every block of four participants with low or high risk of MCI, two were randomly allocated to the exercise group and two to the control group, using a random number generator with outputs "1" for exercise or "2" for control. When a block was filled with two participants from the same intervention group, the next participant randomized to this group was allocated in the next block. In the last block of eight participants, only high MCI risk participants were included, and seven out of eight participants were allocated to the control group. The reason for this decision was to correct for a higher number of dropouts in the high MCI risk control groups at that time. Participants in the exercise group (17 low MCI risk and 14 high MCI risk) took part in a 12-week progressive resistance training program for the lower limbs. Participants in the control group (17 low MCI risk and 22 high MCI risk) did not receive any treatment and were asked not to change their physical activity levels until post-intervention outcome measurements. Assessments and data acquisition at baseline were performed on five different days (Fig. 1) in the following order: (1) blood collection, MoCA test and demographics questionnaire (first visit), (2) MRI scanning (second visit), (3) familiarization of balance and cognitive tests (third visit), (4) balance tests (data not reported in this paper) and cognitive assessment tests (fourth visit), (5) anthropometric measurements and bioimpedance evaluation, handgrip strength assessment, and

measurement of isokinetic and isometric knee extension torque (last visit). All the pre-intervention assessments were completed 1–4 days before the first training session, and all the post-intervention assessments were started 2–4 days after the last training session. Body mass index (BMI) and body fat percentage (fat%) were measured on a leg-to-leg bio-impedance analyzer (Tanita TBF-300-A). Handgrip strength (in kg) was measured using a JAMAR 11940248 adjustable hand grip strength testing system in a standing position. The grip size was adjusted so there was a 90° angle in the second joint of the index finger. The test was preceded by a first try at submaximal effort, followed by two tries at maximal effort with 1-min interval between trials, and the highest value was used for analysis. Maximum isometric knee extension (in Newton meters) exerted by the dominant leg was measured with a Biodex System 3 dynamometer (Biodex Medical Systems, NY, USA). All testing sessions (except MRI) were conducted at the Department of Health Promotion and Rehabilitation, Lithuanian Sports University, and were supervised by a public health specialist (co-author VJC) and an exercise physiology specialist (co-author NM).

2.3. Intervention: progressive resistance training protocol

We implemented a progressive, lower-limb-focused resistance training program that was adjusted based on individual physical abilities. The resistance training protocol was similar to that reported in our previous work (Sheoran et al., 2023; Vints et al., 2024a,c) and was in line with the latest position statement by the National Strength and Conditioning Association (USA) for resistance training for older adults (Fragala et al., 2019). Participants were trained two times per week, with a maximum of two participants per fitness instructor simultaneously. The training sessions took place in the gym at the Lithuanian Sports University using resistance training equipment from Technogym (Italy). Warm-up consisted of 5-min cycling on a cycle ergometer, at an intensity (in Watts) approximately equal to the participants' body weight in kilograms, followed by a few dynamic stretching and activation exercises, including lunges, butt kicks, sidestep lunges, half squats, and front and side cross swings. The main resistance training program consisted of three sets of four lower limb exercises: (1) leg press, (2) leg curl, (3) leg extension, and (4) calf raises. The order of these exercises
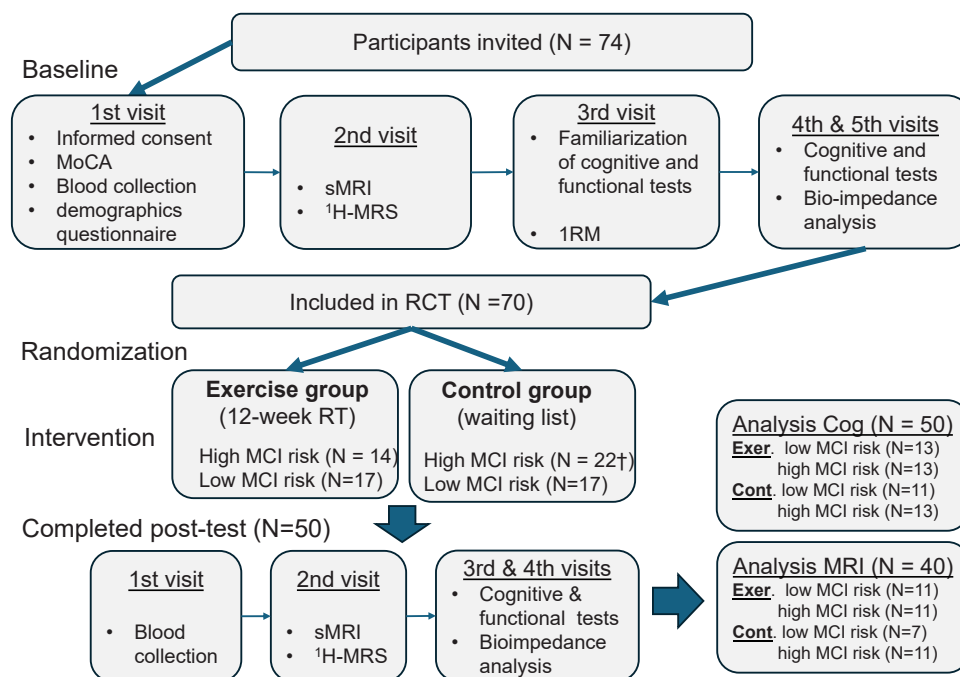

Fig. 1. Experimental flow chart. Abbreviations: MCI = mild cognitive impairment; MoCA = Montreal Cognitive Assessment; RM = repetition maximum; sMRI = structural magnetic resonance imaging; 1H-MRS = proton magnetic resonance spectroscopy.

was not controlled, but in general, the participants were instructed to start with the leg press, as this is a multi-joint exercise, and end with a single-joint exercise such as the calf raises. In the first week of training, the older adults were familiarized with the exercise movements and underwent a 1-repetition maximum (1-RM) test for all four exercises. In the remaining weeks, participants in the exercise group did one warm-up set and three working sets for all four lower limb exercises, with a rest period of 2 min between sets and 3 min between exercises. From week one to three, participants performed 8–10 repetitions at 70–75 % 1-RM, from week four to nine, they worked at 6–8 repetitions at 75–80 % 1-RM, and from week ten to twelve, they performed six repetitions at 80–85 % 1-RM. The weight was adjusted during the three training blocks according to the participants' rate of perceived exertion (RPE) on a 10-point Borg scale (Morishita et al., 2019). The weight was increased when the older adult indicated a score below 7 on a scale of 1–10. The RPE was logged in a notebook by the fitness instructors, along with the number of repetitions and the weight lifted. The resistance training protocol was supervised by qualified fitness coaches, who were not involved in pre-and post-intervention data collection.

2.4. Neurocognitive assessments

2.4.1. MoCA test

The test consisted of 12 items that assessed seven cognitive domains, including visuospatial ability, executive functioning, naming, memory, attention, language, abstract reasoning, and orientation. All items contributed to a score of up to 30 points, with a higher score indicating higher cognitive functioning. The outcome measure was the global MoCA scores recorded at baseline (pre-test) and after 12 weeks of exercise or control (post-test).

2.4.2. ANAM4 test

The assessments of specific cognitive domains comprised of (1) two-choice reaction × (2-CRT), (2) Memory search task, (3) Mathematical processing task, and (4) Go/No-Go task, selected from the ANAM4 (Automated Neuropsychological Assessment Metrics, version 4) test battery (Vista Life Sciences, USA) as previously reported by Vints et al. (2024a). The four tasks included in our study were selected based on previous evidence showing that they are valid for assessing executive functions and attentional processes that can be alleviated by exercise (Engeroff et al., 2018; Herold et al., 2019). All participants were familiarized with the four cognitive tests 48–72 h before the testing day, and all four tests were conducted on the same testing day in a quiet environment. Outcome measures were the response time (in milliseconds) at baseline (pre-test) and after 12 weeks of exercise or control (post-test). Accuracy measures were used to exclude trials with more than 50 % incorrect response, as this may indicate that the participant did not understand the task. In addition, we excluded response times that were faster than the best percentile of young male college students, based on normative values presented in the ANAM4 user manual, considering that this likely indicates that participants did not adequately perform or understand the task and attained the 50 % correct response by chance (ANAM4, 2007). Participants were allowed one practice on each of the four tasks before data recording began. The tasks used are briefly described below:

2.4.2.1. Two-choice reaction time test.
Participants were introduced with a "*" or "o" on the computer display. The participants were instructed to respond as quickly as possible by pressing the left or right mouse button as soon as the stimulus appeared.

2.4.2.2. Go/No-go test.
Participants were presented with two characters, "o" and "x" and were instructed to respond as quickly as possible to the "x" character each time the stimulus appeared. The participants were instructed to withhold their reaction when the character "o"

appears (inhibit response).

2.4.2.3. Memory search test.
The program uses letters and symbols to assess verbal working memory as symbolic and nonverbal subparts. The user viewed a memory set of four letters on the screen (e.g., "T B Q U"). Then, individual characters were displayed, and the participant needed to press mouse buttons to indicate if each character was or was not a member of the positive memory set.

2.4.2.4. Mathematical processing test.
During the test, the participant needed to solve an arithmetic problem (e.g., "4+8-5="). The task involved only three single-digit numbers and two operators. The subject needed to indicate whether the answer is less or higher than five.

2.5. Neuroimaging

Brain imaging consisted of anatomical whole brain MRI and single voxel 1H-MRS at the five voxel locations (data are not presented here) with a total length of about 90 min per participant, as described in our previous studies. All scanning sessions were conducted using a Siemens 3T Skyra Magnetic Resonance scanner (Siemens Healthineers, Erlangen, Germany) with a 32-channel receiver head coil. Three-dimensional high-resolution anatomical images were acquired using T1-weighted Magnetization Prepared Rapid Gradient Echo (MPRAGE) sequence [repetition time (TR) = 2200 ms, echo time (TE) = 2.48 ms, $0.9 \times 0.9 \times 1.0$ mm^3 voxel size, field of view (FOV): 230×256 mm, number of sagittal slices = 176] and co-localized T2-weighted SPACE Dark Fluid sequence [TR = 7000 ms, TE = 394 ms, inversion time = 2100 ms, FOV = 202×256 mm, number of sagittal slices = 176, slice thickness 1 mm]. All scanning sessions were conducted 4–9 days before the cognitive assessment day and were inspected by a senior radiologist to rule out possible structural abnormalities. MRI data were screened for image quality (co-authors MS) to ensure absence of artifacts prior to image processing. Cortical surface area and thickness maps were constructed according to the Destrieux atlas (Destrieux et al., 2010) in an automated manner using the longitudinal pipeline of FreeSurfer (FreeSurfer v7.1.1, Harvard, MA, USA, http://surfer.nmr.mgh.harvard.edu/). The quality of the cortical reconstruction and segmentation was assured by visual inspection (co-author MS) and manually corrected as necessary with the support of quality assurance tools in FreeSurfer (https://surfer.nmr.mgh.harvard.edu/fswiki/QATools).

Between-and within-group cortical thickness comparisons were performed initially for the following parcels of interest: bilateral entorhinal gyri, bilateral inferior parietal gyri, bilateral inferior temporal gyri, bilateral parahippocampal gyri, bilateral rostral middle frontal gyri, bilateral superior frontal gyri, bilateral precentral gyri, and bilateral postcentral gyri (see Fig. 2A). Subsequently, exploratory principal component analysis was performed in R software, version 4.1.3 (R Core Team, 2022). Based on the output of this analysis (see Fig. 2B), two cortical clusters with eigenvalues of over one were defined as principal clusters: (1) the cluster combining the right and left inferiorparietal, inferiortemporal, rostralmiddlefrontal and superiorfrontal cortices and the sensorimotor cortex (fronto-central cluster); (2) the right and left entorhinal and parahippocampal cortices (bilateral hippocampal cluster). Together, these two principal components explained 78 % of the variability. Mean cortical thickness values were extracted for these two principal ROIs as the average cortical thicknesses across all parcels embedded in each cluster. Further inspection of the path diagram of the principal components (Fig. 2B) showed a high factor loading for the right parahippocampal and entorhinal regions; for details, see Supplementary Table S1. Therefore, we conducted an exploratory analysis to examine exercise-induced changes in the left and right parahippocampal and entorhinal regions, separately from the other regions.
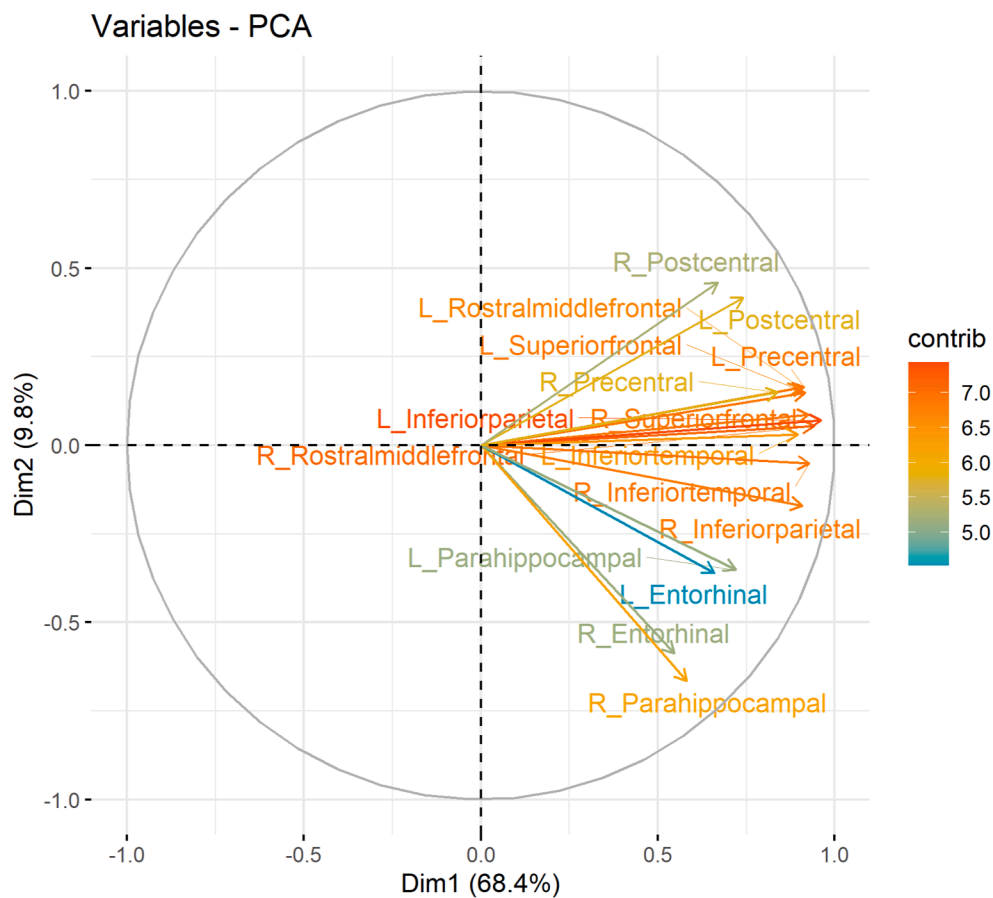
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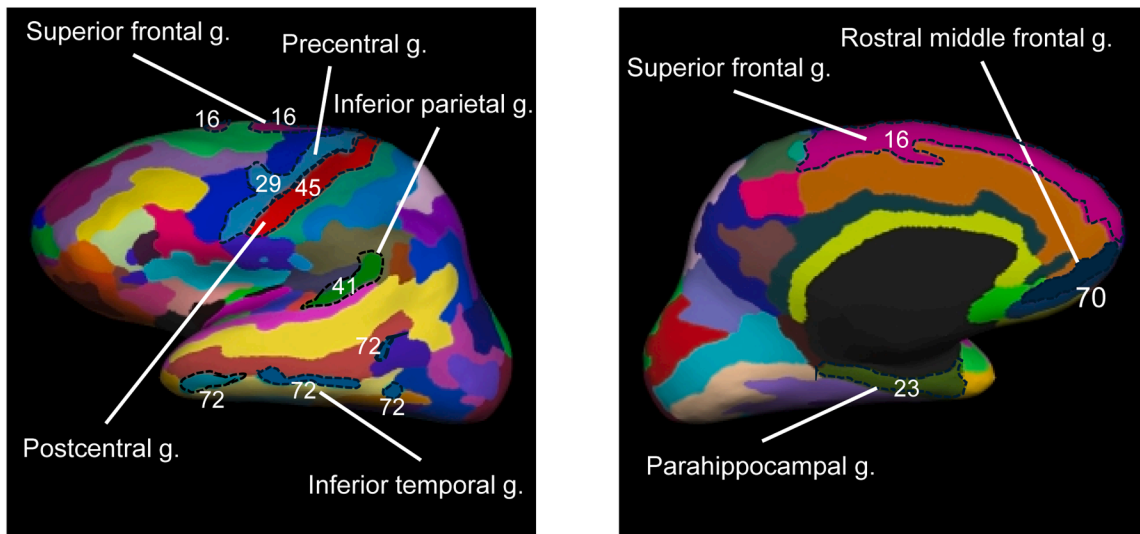
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Fig. 2. (A) Parcelation scheme and parcels of interest. Numerical indices refer to the anatomical regions defined in the Destriuex atlas (Destrieux et al., 2010; https://doi.org/10.1016/j.neuroimage.2010.06.010). (B) Radial plots of the eigenvalues of the correlation matrix of the 16 parcels of interest (L = left hemisphere; R = right hemisphere).

2.6. Confirmatory statistical analysis

All statistical analyses were performed using the open-source software JASP (version 0.16.2; JASP Team, 2022). The effects of 12 weeks of resistance training on cognitive functioning and brain structures in the low and high MCI risk cohorts were analyzed using a set of three-way ANOVAs with Time (2 levels: baseline, post-exercise time points) as repeated measure, and Group (2 levels: Exercise, Control) and MCI Risk (2 levels: high and low) as between-subject factors. Dependent variables for the cognitive domain were the response times on the Choice RT task, Go/No-go task, Memory Search task, and the Mathematical Processing task. Dependent variables for the brain structure metrics were the mean cortical thickness values for the two principal clusters of interest and the cortical thickness of the right parahippocampal cortex. Only significant interactions with the Time Factor were reported. P-values were corrected for multiple comparisons (using either Tukey's post-hoc test in case of significant two- or three-factor interactions with Time or false discovery rate (FDR) in case of exploratory analysis) corrections methods. For all analyses, alpha was set at 0.05.

2.7. Exploratory statistical analysis

Three-way ANOVAs with Time factor as a repeated measure and Group and MCI Risk as between-subject factors were conducted to examine the effects of 12 weeks of resistance training on cortical thickness in the left and right parahippocampal and entorhinal regions. These regions were analyzed separately as they were expected to be more sensitive to structural changes and showed a high factor loading compared to the other pre-selected regions of interest. An exploratory correlation analysis was performed to examine associations between behavioral outcome measures (i.e., reaction time) that were significantly altered by the 12 weeks of resistance training and structural changes in all regions of interest. Finally, we conducted a correlation analysis to explore possible associations between exercise-induced changes in response time on the four cognitive tests and their corresponding response times at baseline.

3. Results

3.1. Participants characteristics

Fifty participants (71.4 %) completed the intervention and underwent blood collection, MRI scanning and cognitive assessments at the post-test time point. Reasons for dropping out were diagnosis with COVID-19 (n = 3), fear of catching a SARS-COV-2 infection, drop out due to pain or injury, fear of injury, lengthy MRI sessions, lack of motivation to complete the training session, or refusal to undergo post-test assessment. The descriptive values of the baseline characteristics for the participants in the exercise group (N = 26, 15 female/11 males), the control group (N = 24, 13 female/11 male), and the total sample of participants (N = 50) who completed data collection are presented in Table 1. Out of the 50 participants, data collected from 40 participants (22 from the exercise group and 18 from the control group) who underwent both pre- and post-intervention MRI sessions were analyzed, and 39 participants had a complete dataset (i.e., cognitive and MRI). Reasons for exclusion were poor MRI data quality or artifacts (n = 10) and missing data on one or more cognitive tests (n = 1); for details, see the project outline and participants flow diagram (Fig. 1) and Supplementary Figure S1. No significant group differences in participants' baseline characteristics or mean outcome measure scores were found (all $p > 0.28$).

To further examine how these dropouts might have influenced the results, a dropout analysis was conducted to compare possible differences in baseline data between participants who completed the intervention and underwent post-intervention tests (completers) and those who did not complete the study (dropouts). Differences between

Table 1
Baseline participant characteristics and group differences.

|	Experimental group	Control group	Total	Group differences (p-value)
N	26	24	50	
Age (years)	70.5	68.7	69.6 (5.9)	0.283
Sex:				0.813[a]
Male	11 (42.3 %)	11 (45.8 %)	22 (44.0 %)	
Female	15 (57.7 %)	13 (54.2 %)	28 (56.0 %)	
Height (m)	1.66 (8.9)	1.68 (7.3)	1.67 (8.2)	0.352
Weight (kg)	78.5 (14.3)	77.3 (11.5)	77.9 (12.9)	0.733
BMI (kg/m^2)	28.6 (4.5)	27.4 (3.3)	28.0 (4.0)	0.297
Fat%	32.7 (9.3)	31.3 (8.1)	32.1 (8.7)	0.584
MoCA score	25.4 (2.5)	24.5 (3.4)	25.0 (3.0)	0.302
MCI risk				0.799[a]
High	13 (50 %)	13 (54.2 %)	26 (52.0 %)	
Low	13 (50 %)	11 (45.8 %)	24 (48.0 %)	
Education:				0.441[a]
Higher	20 (76.9 %)	21 (87.5 %)	41 (82.0 %)	
Secondary	6 (23.1 %)	1 (4.2 %)	7 (14.0 %)	
Basic		2 (8.3 %)	2 (4.0 %)	
Right hand grip force (kg)	32.2 (8.8)	33.7 (11.7)	33.0 (10.2)	0.611
Left hand grip force (kg)	30.0 (8.7)	32.9 (12.5)	31.4 (10.7)	0.369
Right Knee EPT (Nm)	146.1 (44.2)	154.8 (46.9)	150.1 (45.2)	0.518

Continuous parameters are expressed as mean values (SD), p-values are derived from independent t-tests; categorical parameters are expressed as n (% of total), p-values are derived from Mann-Whitney U-test[(a)]. Abbreviatiobs: MoCA = Montreal Cognitive Assessment, BMI = Body mass index, EPT = extension peak torque.

completers and dropouts were analyzed using independent samples *t*-test (normally distributed data) or Mann–Whitney *U* test (if no normal distribution was present or for assessments with an ordinal scale level). No significant differences in demographic characteristics (age, height, weight, BMI, %Fat, and upper/lower limb strength), baseline cognitive status (MoCA), or performance on the four cognitive tests were found (independent samples *t*-test: all $p > 0.41$). In addition, there were no statistical differences in the distributions of gender, level of MCI risk, and level of education (Mann–Whitney *U* test: all $p > 0.16$). Finally, number of dropouts were significantly higher among participants in the control group (n = 15) than in the experimental group (n = 5); Mann–Whitney *U* test ($p = 0.04$).

3.2. Effect of 12 weeks of resistance training intervention on cognitive performance

Data showing the effect of 12 weeks of resistance training on the cognitive performance outcomes at post-test were reported in detail in a previous study (Vints et al., 2024a,b). A significant interaction of Time (baseline vs. post-test) with Group (experimental vs. control) and MCI Risk (high vs. low MCI risk) observed only for response times on the Go/No-go task [$F(1,45) = 6.01$, $p = 0.02$; $\eta_p^2 = 0.12$]; see Fig. 3A for illustration. Further examination of this interaction revealed that older adults with high risk for MCI in the experimental group experienced a slight decrease [$\Delta_{post-baseline} = -4.35$ %, uncorrected $p = 0.08$, Cohen's $d = 0.52$], while those at low MCI risk showed minimal changes (< 1 %) from baseline to post-exercise time point. In contrast, individuals at high risk for MCI in the control group showed no significant change in response time [uncorrected $p = 0.36$, Cohen's $d = 0.28$], whereas those at low risk, showed a decrease [$\Delta_{post-baseline} = -6.83$ %, uncorrected

A Response time on Go/No-go at baseline (pre) and post-test
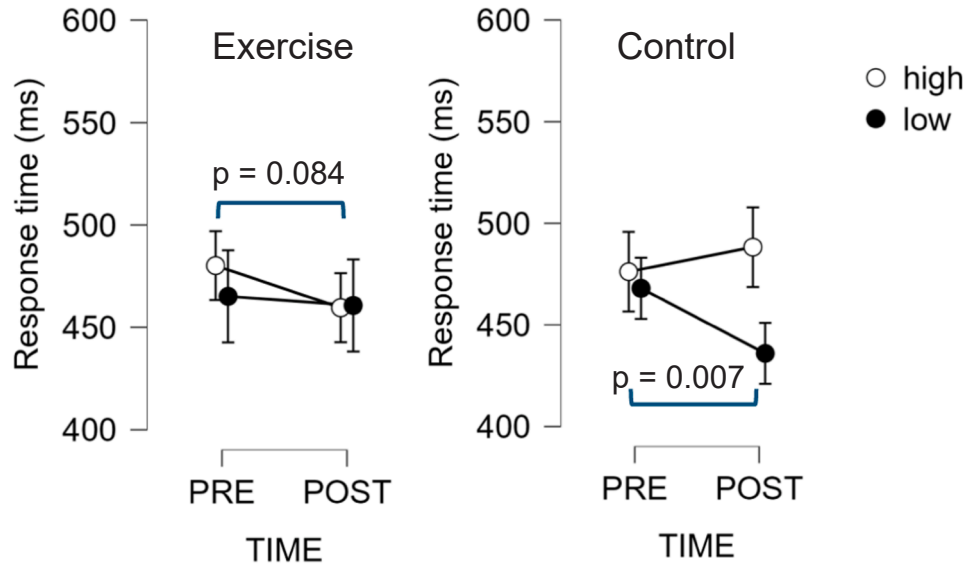
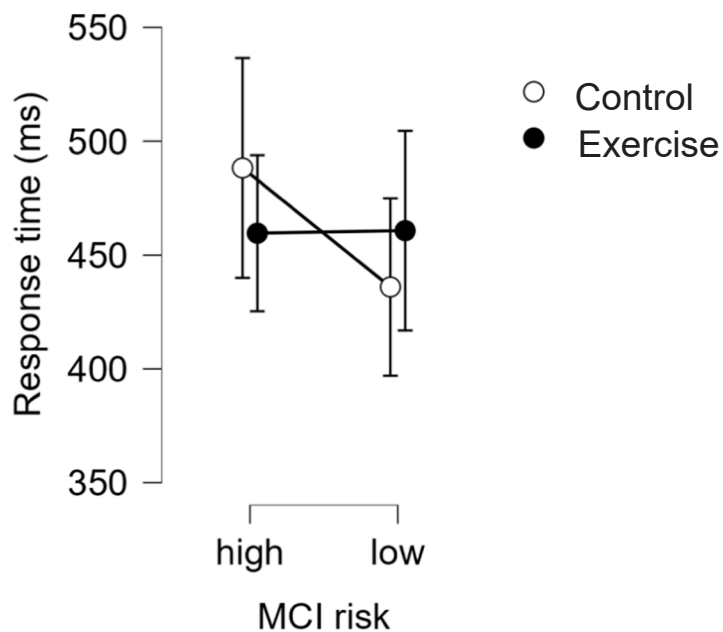**B** Response time on Go/No-go at post-test

Fig. 3. (A) Mean response times on the Go/No-go task at baseline and post-test time points as function of Group (Exercise, Control) and MCI risk (high, low). (B) Mean response time at post-test data point as function of MCI risk and Group. Error bars show the 95 % confidence interval.

p = 0.01, Cohen's d = 1.01]. None of the uncorrected p-values (Fig. 3A) survived FDR correction. The above-mentioned trends were also manifested as differences in post-test between groups and cohorts (Fig. 3B). However, Post-hoc (Tukey) test revealed no significant changes as a function of time, group, or cohort [all, $p_{tukey} \geq 0.23$]. No significant two- or three-way interaction with time were found for the remaining tasks [all, $p \geq 0.128$, $\eta_p^2 \leq 0.05$]. Taken together, the observations illustrated a marginal to-no effect on cognitive performance.

3.3. Effect of 12 weeks of resistance training intervention on average cortical thicknesses

No significant three- or two-way interactions were found for average cortical thicknesses of either the fronto-central cluster or the bilateral hippocampal cluster [F(1,36) ≤ 1.62, p ≥ 0.21, $\eta_p^2 \leq 0.04$]; see Supplementary Table S2. However, results of the three-way ANOVAs revealed a marginal main effect of Group on cortical thickness in the fronto-central cluster [F(1,36) = 3.64, p = 0.06, $\eta_p^2 = 0.09$] and a marginal main effect of the MCI risk on cortical thickness in the hippocampal cluster [F(1,36) = 3.24, p = 0.08, $\eta_p^2 = 0.08$]. Further inspection of the latter suggests that mean cortical thickness at baseline was lower in the high MCI risk cohort [M = 2.80 ± 0.31 mm] than in the low MCI risk cohort [M = 2.94 ± 0.15 mm]. The effects were of a moderate effect size, however not statistically significant [t(38) = 1.85, p = 0.07, Cohen's d = 0.59]. Descriptive values of baseline/12 weeks average cortical thicknesses in the two principal clusters of interest are summarized in Supplementary Table S3.

3.4. Exploratory analysis

3.4.1. Effect of 12 weeks of resistance training intervention on cortical thickness of the parahippocampal and entorhinal regions

A significant Time × Group × MCI Risk interaction was observed for the right parahippocampal region [F(1,36) = 5.3, p = 0.03, $\eta_p^2 = 0.13$], but not for the left parahippocampal or left and right entorhinal regions (see Supplementary Table S2). Post-hoc (Tukey) test revealed no statistically significant baseline to post-test changes or group differences relating to this interaction [all, $p_{tukey} \geq 0.29$]. However, some trends were found, suggesting a differential response to intervention between high and low MCI risk subgroups (Fig. 4). Older adults with high MCI risk allocated to the experimental group showed an increase in parahippocampal cortical thickness [$\Delta_{post-baseline}$ = +1.18 %, uncorrected p = 0.08, Cohen's d = 0.60] whereas no visible exercise-induced changes were found for older adults with low MCI risk. In contrast, older adults with high MCI risk who were allocated to the control group showed no pre-to-post changes in parahippocampal cortical thickness, whereas a trend showing an increase in parahippocampal cortical thickness was observed in older adults with low MCI risk [$\Delta_{post-baseline}$ = +2.19 %, uncorrected p = 0.01, Cohen's d = 1.44]. None of the uncorrected p-values survived FDR correction. Descriptive values of baseline/12 weeks average cortical thicknesses in left/right parahippocampal and entorhinal cortices are summarized in Supplementary Table S3.

3.4.2. Structural correlates of performance changes on the Go/No-go task

Exploratory correlational analyses were completed to examine whether cortical thickness changes from baseline to post-test predicted
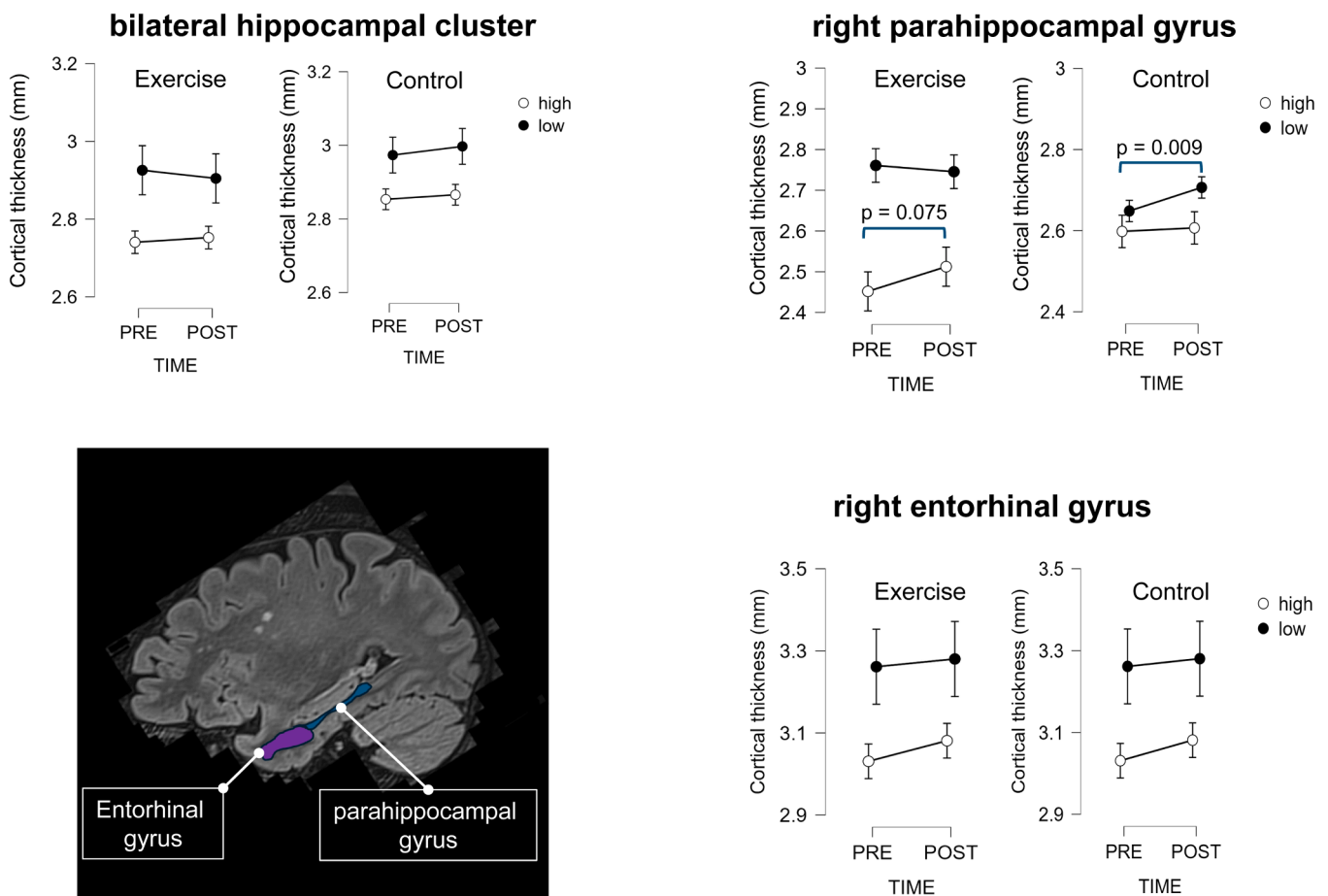

Fig. 4. Mean cortical thickness of the bilateral hippocampal cluster, right parahippocampal gyrus and right entorhinal gyrus at baseline and post-test time points as function of Group and MCI risk.

performance changes on the Go/No-go task. For the exercise group, a negative association was found between response time on the Go/No-go task and cortical thickness changes in the right entorhinal cortex [r = -0.57, uncorrected p = 0.01] (Fig. 5 and Table 2); for details see Supplementary Table S4. A similar negative trend was found for the control group. The decreased response time on the Go/No-go task from baseline to post-test for the control group was associated with increased cortical thickness in the right parahippocampal cortex [r = -0.57, uncorrected p = 0.02]. Further examination of these findings indicated that these trends were found only in individuals with low MCI risk. Exercise group: Go/No-go response time with right entorhinal cortical thickness [r = -0.64, p = 0.03]. Control group: Go/No-go response time with right parahippocampal cortical thickness [r = -0.81, uncorrected p = 0.03]. None of the correlations survived the FDR correction.

3.4.3. Effect of baseline performance

Results showing the correlations between exercise-induced changes in response time on the four cognitive tests and their corresponding response times at baseline are shown in Table 3 for the exercise group. Overall, observations from this exploratory analysis showed that changes in reaction time were negatively associated with baseline reaction times. However, all correlations were of moderate effect size, ranging between r = -0.31 (for Go/No-go) to r = -0.40 (for Mathematical processing), with the two other tasks positioned in between. None of

Table 2
Bivariate associations between changes in response time on the Go/No-go test and cortical thickness changes in right entorhinal and parahippocampal gyri.

	n	r	p-value (uncorrected)
Right entorhinal gyrus			
Exercise, total	22	−0.571	**0.006**
Exercise, high MCI risk	11	−0.464	0.150
Exercise, low MCI risk	11	−0.639	**0.034**
Right parahippocampal gyrus			
Control, total	17	−0.571	**0.017**
Control, high MCI risk	10	−0.305	0.392
Control, low MCI risk	7	−0.809	**0.028**

the correlations survived the FDR correction.

4. Discussion

The effects of 12 weeks of resistance training on structural characteristics of brain regions associated with higher executive control functions and memory performance were studied in older adults with low and high risk of MCI. We focused specifically on exercise-induced changes in cortical thickness of subregions that are anatomically and physiologically connected to the hippocampus and/or prefrontal/parietal subregions prone to structural declines in cognitive aging and MCI. Our findings showed no direct effects of the intervention on the
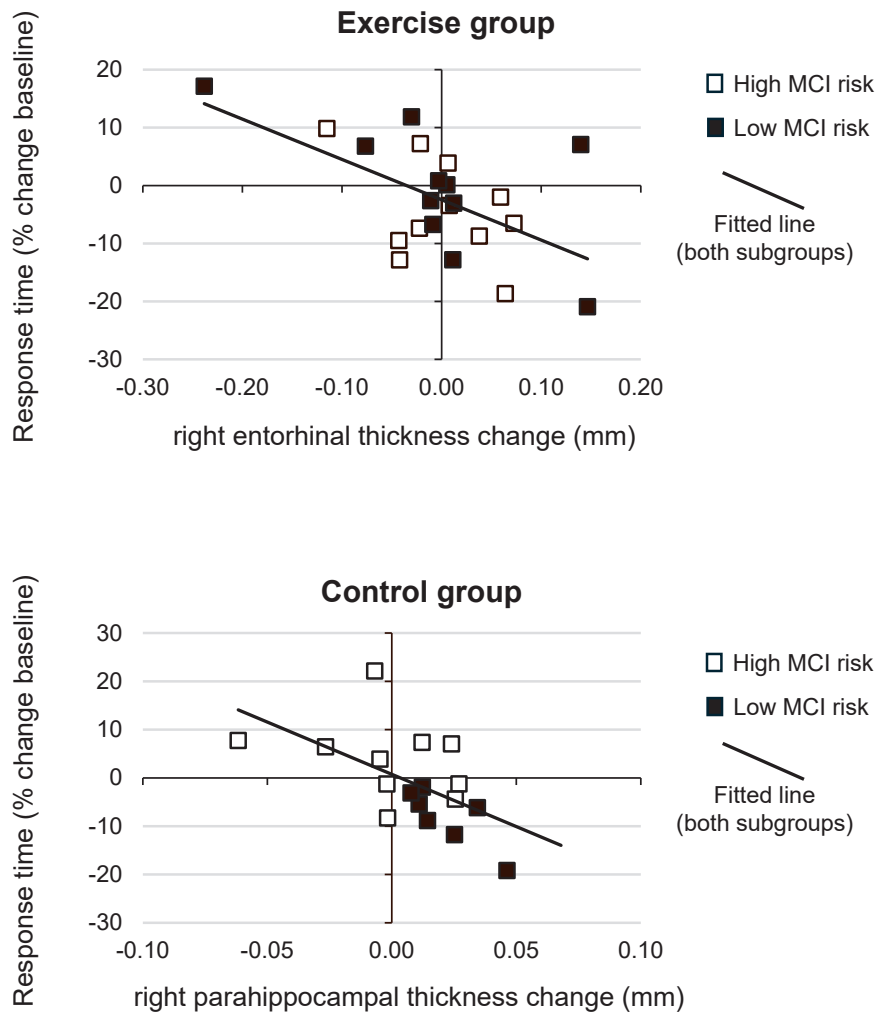

Fig. 5. Bivariate relationship between pre-to-post changes in the cortical thickness of right entorhinal (upper panel) and parahippocampal (lower panel) gyri and changes in ANAM Go/No-go response time (ms) in the experimental group as function of MCI risk. Positive values mark increases from pre- to post test. Abbreviations: ANAM = Automated Neuropsychological Assessment Metrics; MCI = mild cognitive impairment.

Table 3

Bivariate correlations between exercise-induced changes in response time on the cognitive tests and their corresponding response times at baseline.

n = 26	Δ2CRT	ΔGo/No-go	ΔMemory search	ΔMathematical processing
2CRT	r = −0.379 p = 0.056			
Go/No-go		r = −0.306 p = 0.129		
Memory search			r = −0.391 P = 0.048†	
Mathematical processing				r = −0.399 p = −0.044†

Abbreviations: 2CRT = 2-choice reaction time tests.
†FDR threshold p-value = 0.0125.

structural properties of the analyzed cortical areas. However, despite the lack of statistical significance, the moderate effect size (Cohen's d = 0.60) suggests a small increase in right parahippocampal cortical thicknesses from baseline to the post-test in participants with high MCI risk in the resistance-training group (+1.2 %). In contrast, we detected a large effect size (Cohen's d = 1.44), suggesting an increase in right parahippocampal cortical thicknesses from baseline to the post-test in participants with low MCI risk in the control group (+2.4 %). Finally, evidence for associations between cortical thickness gains and cognitive performance gains in the exercise group was found only in the low MCI risk group and was observed predominantly between response times on the Go/No-go or 2-CRT tests and subregions of the right hippocampal cluster. Our findings reveal no evidence for intervention-induced changes in cortical thickness of other brain regions or clusters examined in the present study.

Concerning the differential effect of cognitive status on the findings, we observed that older adults with high MCI risk were generally more responsive to exercise than those with low MCI risk, suggesting that the beneficial effects of exercise were more pronounced in older adults with high cognitive loss. On the one hand, this observation strengthens evidence from previous studies, e.g., (Zhang et al., 2020; Tsai et al., 2019), showing that resistance training is likely to be more efficient for improving cognitive functioning in older adults with lower cognitive skills, such as older adults with MCI. On the other hand, differences between the two MCI risk subgroups at the post-test were not statistically significant after FDR corrections. Further, we did not find significant correlative relationships between response times at baseline and their corresponding exercise-induced changes, suggesting that the interplay between cognitive status and exercise-induced cognitive gains was not task-specific. Finally, it is essential to realize that the total number of participants with a complete dataset (i.e., 22 from the exercise group with 11 high MCI risk, and 17 from the control group with 10 high MCI risk) was too low for sufficient statistical power. Therefore, the present study's findings should be carefully interpreted and regarded as pilot observations to be replicated in a large sample.

There are several confounding factors, such as differences in the type of cognitive task, that can explain the mixed effects of exercise intervention on cognitive outcomes. For example, tasks that are too easy or too difficult may not be sensitive enough to reveal exercise-induced differences. In addition, gains in cognitive performance may have been masked by cognitive status and level of baseline cognitive skills. However, it can be seen from Table 3 that negative relationships between performance gains and baseline performance levels across the four cognitive tasks were of a similar order, suggesting that training effects were homogeneous. Results can also be explained based on neurobiological mechanisms of muscle-brain cross-talk that were discussed in our previous work (Sheoran et al., 2023; Vints et al., 2024a,c). For example, findings from the study of Sheoran et al. (2023). on a subset of participants that were included in the present study showed that gains in peak knee torque were positively related to increases in the expressions of brain neurometabolites such as N-acetyl-aspartate (NAA)

and myo-inositol (mIns) across multiple brain regions. The latter finding is important, as it suggests that resistance training is not only localized to the specific muscles being trained but concurrently leads to enhanced brain neuronal health. The fact that this observation was not restricted to specific functional subregions could possibly be a marker of a general (rather than a differential) effect of exercise on brain function.

The findings of the present study can be discussed considering evidence from blood-sample and MRI/^{1}H-MRS studies conducted on the same group of participants (or on a subset of them), revealing associations between exercise-induced changes in circulating biomarkers and cognition (Vints et al., 2024a) or pre-to post-test changes in hippocampus volume and neurometabolic status (Vints et al., 2024c). Observations from these two studies revealed nonetheless complex patterns of interactions between markers of brain health, circulating biomarkers, and cognitive performance changes. For example, it was found that exercise-induced volumetric gains in the hippocampus (or its subfields) were associated with a decrease in serum levels of inflammatory biomarkers (i.e., kynurenine and IL-6) (Vints et al., 2024a) but not with increased levels of the neurotrophic factor IGF-1 which was found to be associated positively with performance gains (Vints et al., 2024a). In addition, it was found that participants in the resistance exercise group tended to show an increase in hippocampus NAA to creatine ratio (considered as a marker of neuronal viability). However, the latter was accompanied by an increase in the ratio of mIns to creatine which could suggest an increase in glial cell activation and neuroinflammation (Vints et al., 2024c). The combined findings from the present study and our previous research suggest that 12 weeks of resistance training can potentially prevent neuronal loss in the hippocampal complex, confirming its potential neuroprotective effect. However, given that findings from the present study and the two other studies (Vints et al., 2024a,c) revealed only minor structural and cognitive gains, we suggest that the duration of the intervention is too short. The supposition is consistent with the results of recent meta-analyses showing that exercise training had beneficial effects on the cortical structure and hippocampal volume when the intervention duration lasted 24 weeks or more, e.g (McEwen et al., 2023; Wilckens et al., 2021a).

The role of intervention duration and volume as moderators of exercise-induced effects on performance has been addressed in a few recent meta-analyses suggesting that intervention periods of at least 12 weeks of moderate to vigorous resistance training can generally improve cognitive functions (Cheng et al., 2022; Ali et al., 2021). For example Cheng et al. (2022) concluded that, to improve cognitive functioning effectively, the intensity of the resistance training exercise should be moderate to high, and the intervention duration should last longer than six months. Results from other meta-analyses suggest that cognitive gains produced by moderate exercise with medium or longer intervention durations may not differ statistically from cognitive gains that were found after training periods equal to or shorter than 12 weeks (Northey et al., 2018; Zeng et al., 2023). Furthermore, it has been suggested that the frequency and intensity of the intervention rather than its duration would be the main contributing factors for cognitive improvements. The resistance training protocol in the present study included vigorous exercise intensity (70–85 % 1RM with 10–6 repetitions per set) with an exercise duration of 45 min and a frequency of 2–3 days/week for 12 weeks. This protocol is considered effective for inducing cognitive gains in older adults (Northey et al., 2018).

The observation that changes were found only for response time of the Go/No-go test and were more pronounced in older adults with high MCI risk suggests that resistance training may be more beneficial for improving response inhibition. This observation was confirmed by multiple meta-analyses showing that executive functions were generally more responsive to resistance training than memory functions (Zhang et al., 2020, 2023b; Landrigan et al., 2020). However, this interpretation should be read with care as performance gains on the Go/No-go task were also observed in older adults with low MCI risk that were allocated to the waiting list (passive) control group (Fig. 3). Finally, psychological

confounding factors that can lead to a better post-test performance gain in the exercise group compared to control such as a higher expectation to improve should be considered. Therefore, future studies should employ an active control group engaging in exercise activities with similar expectations to improve cognitive performance as the experimental group (Ziv et al., 2024).

As a main finding of this study, we describe the negative correlation between changes in response time on the Go/No-go test and changes in right entorhinal cortical thickness in the exercise group (Fig. 5A). This observation is consistent with evidence that physical exercise training can significantly alter the structural and functional integrity of the hippocampus and its related cortical structures, leading to pre-to post-intervention gains (Vints et al., 2024c; Erickson et al., 2011; Maass et al., 2015; Pani et al., 2021; Raji et al., 2024; Chen et al., 2020; Wilckens et al., 2021b; Rosano et al., 2017); for reviews (Chen et al., 2020; Ji et al., 2021). The fact that our intervention did not result in significant thickening of the right entorhinal cortex could be explained in part by exercise-induced strengthening of existing neural connections through long-term potentiation or synaptogenesis rather than the formation of new connections (Vints et al., 2022a).

In this respect, it is important to note that intensive resistance training can significantly increase the expression of pro-inflammatory cytokines (Senna et al., 2022), and/or changes in the gene expression of inflammation-related genes (Liberman et al., 2022). This could explain in part the overall absence of changes in cortical thickness observed in the exercise group and the marginal increase of cortical thickness in the parahippocampal region observed in the control group as shown in Fig. 4B. Finally, (Vints et al., 2024c) revealed a negative association between higher IL-6 levels and volume loss in the cornu ammonis 4 (CA4) subregions of the hippocampus. This observation suggests that increased expression of IL-6 was associated with volume loss in the exercise group. The finding above supports the supposition that the release of cytokines during the early phase of the intervention could delay the onset of neuroplasticity and result in performance decrement (da Rocha et al., 2019). Further studies should be carried out in order to identify the effects of exercise intensity and duration of the intervention on inflammation response occurring in the aging brain as well as their possible dose-response effects on the complex interplay between neuroinflammation and neuroplasticity (Vints et al., 2022b; Macaulay et al., 2022).

The present study has some limitations. First, the intervention period of 12 weeks may have been too short to observe meaningful changes in the measured brain and performance outcomes. Furthermore, interaction effects were small and were difficult to interpret. Second, the study suffered from high dropout rates. Our dropout analysis showed that most dropouts were in the control group, suggesting that participants have adhered to the intervention. Out of the five participants who did not complete the intervention, only three quit the study due to injury or fear of injury. The two other participants were infected by COVID-19 but underwent post-test measurements as a separate subgroup (Vints et al., 2024b). Adherence within the control group was lower (61.5 %) and was attributed mainly to not attending post-tests. It is therefore suggested that including an active control group would be preferable as an alternative. Finally, exploration of additional cognitive and neuro-imaging measures of white matter structural properties, as well as mediation analyses of putative working mechanisms (e.g., inflammation), are expected to provide a more comprehensive understanding of resistance training's effects on brain health. Nonetheless this would require a larger sample size than that available in the present study.

To conclude, our observations suggest that 12 weeks of resistance training could be beneficial but not sufficient to induce a widespread increase in the cortical thickness of brain regions susceptible to age-related gray matter atrophy. Further studies should be conducted with a larger sample size, longer intervention duration, various exercise intensities, and active control group to re-examine the research hypothesis for beneficial effects of resistance training on brain structure and

cognitive outcome measures in older adults with high MCI risk. Last but not least, researchers should focus on understanding the moderating role of intervention volume and duration in the interplay between inflammatory and neurotrophic processes.

Funding

Author contributions

Simona Kušleikienė, Gal Ziv, Wouter Vints, Orgesa Qipo, Ivan Bautmans, Uwe Himmelreich, Nerijus Masiulis, Vida Česnaitienė, and Oron Levin contributed to conception and design of the study. Simona Kušleikienė, Vida Česnaitienė, and Nerijus Masiulis were involved in management of the RCT. Milda Šarkinaite was involved in acquiring and analysing of MRI data. Simona Kušleikienė, Gal Ziv, Erika Krasinskė and Oron Levin performed/supervised the statistical analysis. Simona Kušleikienė, Gal Ziv and Oron Levin wrote the first draft of the manuscript. Oron Levin, Uwe Himmelreich, Ivan Bautmans, and Nerijus Masiulis had a role in supervision. All authors contributed to manuscript revision, read and approved the submitted version.

CRediT authorship contribution statement

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Declaration of Competing Interest

There are no other competing interests to declare.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.brainresbull.2025.111249.

Data availability

Data will be made available on request.

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