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No long-term benefits from resistance training on brain grey matter volumes in active older adults at retirement age

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Abstract

Background Resistance training and other forms of physical exercise are commonly suggested to promote brain health, yet the relationship between resistance training and brain structure in aging is poorly understood. We examined the short- and long-term influence of one year of supervised resistance training at two different loadings on brain structure in aging.

Methods In the LISA (LIve active Successful Ageing) study, well-functioning older adults at retirement age (mean age: 66 ± 2 years) were randomized to one year of heavy resistance training (HRT), moderate intensity training (MIT), or a non-exercising control group (CON). Magnetic resonance imaging (MRI) of the brain was performed at baseline, 1-, 2-, and 4-years follow ups. Trajectories of total grey matter, hippocampus, dorsolateral prefrontal cortex (dlPFC), ventrolateral prefrontal cortex (vlPFC), and white matter hyperintensities were analyzed in relation to changes in muscle strength.

Results Individuals ($n = 276$) with MRI scans at all 4 timepoints were included (HRT, $n = 96$; MIT, $n = 95$; CON, $n = 85$). Total grey matter volume decreased with time across all groups ($F_{3,819} = 231.549$, $p < 0.001$, $\eta^2 = 0.46$), as did hippocampal ($F_{3,819} = 310.07$, $p < 0.001$, $\eta^2 = 0.53$), vlPFC ($F_{3,818} = 74.380$, $p < 0.001$, $\eta^2 = 0.21$), and dlPFC ($F_{3,818} = 3.640$, $p = 0.013$, $\eta^2 = 0.01$) volumes. White matter hyperintensity volumes increased ($F_{3,819} = 101.876$, $p < 0.001$, $\eta^2 = 0.27$). There were no significant group x time interactions for any of the brain structures. Additional cortical and subcortical vertex-wise analyses showed no group differences. Change in isometric leg strength was weakly associated with change in white matter hyperintensity volume across all individuals ($r^2 = 0.01$, $p = 0.048$).

Conclusions One year of resistance training in well-functioning older adults at retirement age did not influence volume changes in selected brain regions over a 4-year period.

Trial registration The study was approved by the regional ethics committee and registered on clinicaltrials.gov 2014–04-24 (NCT02123641).

Keywords Resistance training, Exercise, Older adults, Aging, Brain health, Magnetic resonance imaging, Grey matter volume, White matter hyperintensity, Muscle strength

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Background

The beneficial effects of resistance training on general physical health and aging are well known and have been studied substantially [1, 2]. In relation to brain health, there are, surprisingly, only a few studies, although it has been encouraged for more than a decade [3]. In a small sample of healthy young adults, 4 weeks of unilateral leg resistance training induced some changes of white matter microstructure and putamen volume [4]. In older adults, improved muscle function following 12 weeks of resistance training seemed to preserve brain metabolism [5], and prolonged resistance training (52 weeks) attenuated brain atrophy [6]. It has also been proposed that prolonged resistance training could be beneficial for cognitive functions [7–9]. Moreover, in the oldest old (85 years old or above) it has been speculated that combining aerobic and resistance training could provide a synergistic effect [10]. Despite of these initial positive results, the knowledge on brain structural changes following resistance training is much sparser in comparison to what is known of other modes of exercise, such as cardiorespiratory training [11].

Regardless of training modality, less focus has been on the potential long-term effects of an exercise intervention on brain health. One exception is the Generation 100 study [12]. In this large long-term study, the effects of a 5-year exercise intervention at different intensities were investigated. The brain imaging results suggested that a high cardiorespiratory fitness level at study start and following the national activity guidelines was related to preserved brain structure rather than training at high intensity [13]. Similar observations were made for the neurochemical profile of the hippocampus [14] as well as the development of white matter hyperintensities, which was not attenuated by taking part in the prolonged supervised training [15]. The Generation 100 study underlines how important it is to follow individuals over time also in relation to physical training interventions. In a similar attempt the LISA study was initiated [16]. Here, a 1-year resistance training intervention at two different loadings (moderate vs heavy) has been compared to a non-exercising control condition. So far, the results have shown that muscle strength was improved [17] and maintained at the 2-year follow up [18] but there was no effect of the training intervention on hippocampal atrophy at either of these time-points.

It is well documented that although aging may affect the brain globally [19], some regions are more prone to show atrophy such as the hippocampus [20] and the prefrontal cortex [21], which has been further associated with cognitive aging [21, 22]. Notably, physical exercise has shown positive effects in relation to hippocampal volume atrophy [23], improved memory [24], prefrontal cortex grey matter volume and executive functions [25].

Thus, the aim of this study was first to examine how one year of resistance training at two different loadings influenced brain volumes globally and in atrophy-prone regions and second to test whether the long-term maintenance of muscle strength present at both the 2-year follow up [18] and at the 4-year follow up [26] was associated with brain structural changes.

Methods

The LISA (LIve active Successful Ageing) study is a large-scale randomized controlled trial based at a university hospital, with a 1-year intervention and longitudinal follow-ups at years 2, 4, 7 and 10. The study adhered to CONSORT guidelines and the full study protocol has previously been published [16]. To outline, 1026 older adults were screened after recruitment through advertisements in local media. Of these, 451 individuals underwent pre-testing and were subsequently included in the study. The participants were volunteering, home-dwelling, older adults around retirement age, 62–70 years (mean age: 66 years; 61% women), and were not allowed to undertake systematic resistance training prior to the study. The participants were rather active, with an average daily physical activity level of almost 10.000 steps/day, although ≈ 80% had at least one chronic disease [17]. Participants were stratified based on age, body mass index (BMI), and performance in the chair-rise test and randomized to one of three intervention groups: heavy resistance training (HRT, $n=149$), moderate intensity training (MIT, $n=154$), or a non-exercising control group (CON, $n=148$). HRT and MIT trained 3 times per week. HRT trained in two local commercial gyms, where training was supervised in small groups and performed as a machine-based full body programme, with a focus on the lower extremities. Training was progressed and linearly periodized, with one week of rest every 9th week. In the moderate intensity training, exercises were performed with bodyweight and resistance bands once weekly at a facility at the hospital and twice weekly at home, with training progressed similarly to HRT. When the 1-year intervention was completed, no further training was offered to the participants. Training-compliance was relatively high, 77% and 78%, respectively. For specific exercises, intensity, and volume in the two training groups, see previous publications [16, 17]. Individuals in the non-exercising control group were asked to maintain their habitual physical activity level and were allowed to perform a maximum of 1 h of systematic strenuous physical activity per week during the 1-year intervention. Individuals randomized to this group were offered cultural and

social activities, e.g., bridge sessions, lectures, or walks, on average once per month.

In total, three separate days were allocated for assessments. On day 1, a short and basic medical examination was performed including anthropometric measures and blood samples in the fasted state. An accelerometer was attached and worn for 5 days, and photographs of body and face for perception of age were collected. The second day, which was scheduled a minimum of 6 days after the first day, started with dual-energy x-ray absorptiometry (DXA) scans for body composition. Cognitive ability was assessed with a shortened Danish version of the intelligence structure test IST-2000-R [27], containing 3 subtests of 6, 7 and 10 min respectively, as previously used in three different Danish cohorts [28]. Finally, tests of physical function including 400 m walking time, 30 s chair-rise test, leg extensor power, handgrip strength, and maximal isometric leg strength were performed. For the third and last day of assessments, magnetic resonance imaging (MRI) of the brain and thigh was acquired using a 3.0 Tesla scanner (TX Phillips Achieva Scanner, Philips Healthcare) at the Danish Research Centre for Magnetic Resonance (DRCMR) at Hvidovre Hospital, Denmark. Participants were asked to refrain from strenuous physical activity in the preceding 72 h. All scans were performed by an experienced radiographer. The images were used to estimate the cross-sectional area (CSA) of m. vastus lateralis as well as to segment the brain into selected regions of interest (ROI) using the FreeSurfer software (version 6.0).

The automatically generated volumes were used to obtain total brain grey matter, white matter hyperintensities, and hippocampal volume. For the volume of dorsolateral prefrontal cortex (dlPFC) the 'caudal-middle-frontal' ROI was used [29] while 'pars opercularis', 'pars orbitalis', and 'pars triangularis' ROIs were combined for the ventrolateral prefrontal cortex (vlPFC) volume [30]. For all regions, the sum of the left and right hemisphere was used.

Vertex-wise general linear models served to test for group differences in the annual rates of change in cortical thickness, cortical surface area, and subcortical volumes. First, Freesurfer's longitudinal pre-processing pipeline was applied [31]. For cortical thickness and area, we (1) reduced the temporal data within each subject to a single statistic (annual rate of change), and then (2) compared the rate of change across RCT groups using general linear models, with one contrast for each group comparison, and including sex as a covariate. Surface maps were then registered to the standard average space and smoothed with a Full Width at Half Maximum (FWHM) of 10 mm. Freesurfer's precomputed Z Monte Carlo simulations (mri_glmfit-sim) were applied to set the vertex-wise threshold, whereby uncorrected p-value surface maps were thresholded at $p < 0.001$ (i.e. cluster-defining threshold of 3.0; [32]). The cluster-wise p-value was set at the $p < 0.05$ level, and p-values were adjusted for the 2 hemispheres.

Finally, we tested if the rate of volume changes in subcortical structures differed between groups by applying "long_stats_slopes" and the same general linear model as described above (including sex as a covariate). Multiple comparisons were applied using Bonferroni.

Due to contraindications for MRI (e.g., pacemakers, other metallic components, claustrophobia) not everyone included in the LISA-study took part in the MRI. See Fig. 1 for a study flow chart. For the present study, 276 individuals had MRI scans at all 4 timepoints (HRT, $n = 96$; MIT, $n = 95$; CON, $n = 85$). See Table 1 for characteristics at baseline and year 4.

Statistical analysis

All statistical analyses were performed in R version 4.1.1 and Rstudio 2021.09.0 using "psych" [33], "dplyr" [34], "emmeans" [35] and "sjstats" [36] packages. Figures were created in GraphPad Prism version 10.0.3.

Student's paired t-tests were used to test potential changes over the 4 years in participant characteristics for each group. For these participant characteristics two-way ANOVAs were computed to test for group x time interactions. Two-way mixed model ANOVAs were used to test for group x time interaction on brain structure (total grey matter volume, hippocampus, dorsolateral prefrontal cortex, ventrolateral prefrontal cortex, and white matter hyperintensity volume). These analyses were corrected, in the model, for estimated total intracranial volume and sex. Adding baseline levels as a covariate did not alter the results.

Associations between Δ-change in muscle strength (baseline to year 4) and Δ-change in brain structures (baseline to year 4) were tested with partial correlation analysis. The significance level was $p < 0.01$ after Bonferroni correction for multiple comparisons across the five brain outcomes.

Effect sizes are reported in the form of eta squared (η^2) for interactions and r^2 for change-change correlations.

Results

As shown in Table 1, at the 4-year follow-up assessments, participants were on average 71 years of age. The amount of daily physical activity was still high with an average daily step count of nearly 10,000 in each of the groups.

There were no differences between groups at baseline for any of the brain variables. Across time, there were no differences, i.e., no significant group x time interactions, in change between the three groups (HRT, MIT, CON)

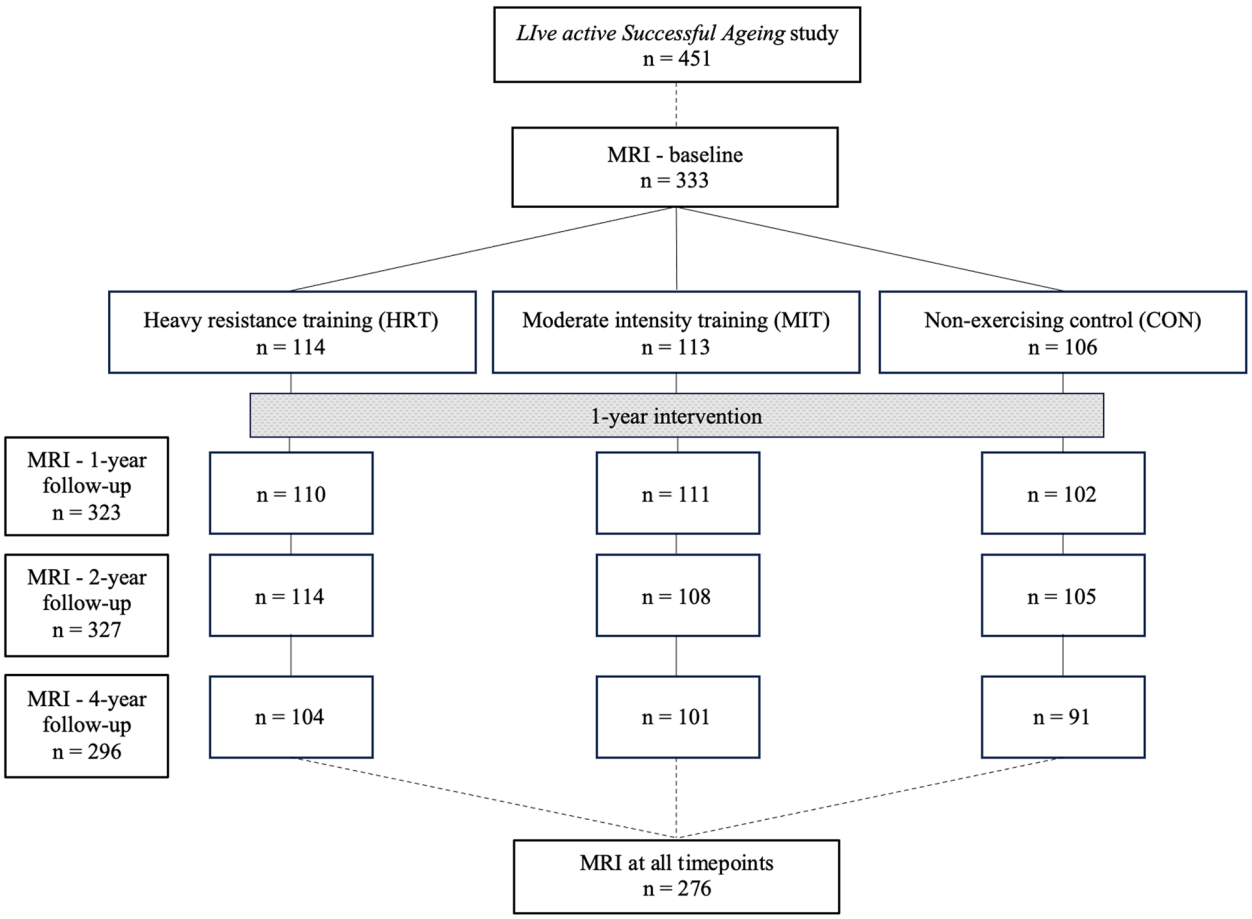

Fig. 1 Study flow chart with participants taking part in the MRI

in the pre-specified brain variables (total grey matter volume, white matter hyperintensities, hippocampus volume, dlPFC volume and vlPFC volume). See Table 2.

The changes over the 4 years are displayed for each group respectively in Fig. 2A-E.

For total grey matter volume, there was a significant effect of time, with a decrease over the four years ($F_{3,819}=231.549$, $p<0.001$, $\eta^2=0.46$). This was similar for hippocampal volume ($F_{3,819}=310.07$, $p<0.001$, $\eta^2=0.53$), where the decrease from 2-year follow-up to 4-year follow up (~1.7%) was at a rate similar to what has previously been described from baseline to year 2 (0.8% during each of the first two years). Likewise, there was a decrease in volume over time for vlPFC ($F_{3,818}=74.268$, $p<0.001$, $\eta^2=0.21$), as well as for dlPFC ($F_{3,818}=3.638$, $p=0.013$, $\eta^2=0.01$). The increase in volume of white matter hyperintensities ($F_{3,819}=101.876$, $p<0.001$, $\eta^2=0.27$) corresponded to ~7–8% annually across all groups. Despite the group-dependent change in leg muscle strength over time, there were no significant group x time interactions for any of the brain structures.

The surface-based group analyses of cortical thickness and surface area revealed no significant clusters at the chosen vertex-wise threshold. Likewise, there were no significant group differences in annual rate of change in subcortical volumes – see Supplementary Table 1. Similar analyses of the intervention (baseline to year 1) showed comparable results (Supplementary Table 2). Thus, for none of the brain variables, neither the pre-selected specific volumes, the global measures of brain changes, nor the vertex-wise analysis (at the pre-specified significance thresholds), was there any indication that resistance training or intensity modified the change over time.

The association between leg muscle strength and white matter hyperintensity volume is shown in Fig. 3. Changes over the four years were negatively correlated ($r^2=0.01$, $p=0.048$). When the same association was tested for each group separately, changes over the four years were negatively correlated for CON ($r^2=0.06$, $p=0.029$), but not for HRT ($r^2=0.03$, $p=0.119$) or MIT ($r^2=0.002$, $p=0.653$). However, associations were not significant after correcting for multiple comparisons ($p>0.01$).

Table 1 Sample characteristics (mean ± SD), $n = 276$, at baseline and year 4 for each group: HRT, heavy resistance training; MIT, moderate intensity training; CON, non-exercising control group

	HRT $n = 96$			**MIT** $n = 95$			**CON** $n = 85$			
	Baseline	**4-year**	**T-test**	**Baseline**	**4-year**	**T-test**	**Baseline**	**4-year**	**T-test**	**F (group x time)**
Sex (m/w, %)	41/59	41/59	-	37/63	37/63	-	38/62	38/62	-	-
Age (years)	66.4 ± 2.6	70.5 ± 2.6	$t(95) = 1.99$ $p < 0.001$	66.4 ± 2.4	70.5 ± 2.5	$t(94) = 1.99$ $p < 0.001$	66.6 ± 2.5	70.7 ± 2.4	$t(84) = 1.99$ $p < 0.001$	$F_{2,273} = 14.21$ $p < 0.001$, $\eta^2 = 0.09$
Weight (kg)	76.3 ± 13.0	75.5 ± 13.4	$t(95) = 1.99$ $p = 0.051$	74.6 ± 11.9	73.8 ± 12.3	$t(94) = 1.99$ $p = 0.035$	74.4 ± 12.7	74.8 ± 13.8	$t(84) = 1.99$ $p = 0.401$	$F_{2,273} = 2.685$ $p = 0.070$, $\eta^2 = 0.02$
BMI (kg/m^2)	25.8 ± 3.9	25.8 ± 4.0	$t(95) = 1.99$ $p = 0.986$	25.6 ± 3.6	25.5 ± 3.8	$t(94) = 1.99$ $p = 0.577$	25.4 ± 3.5	25.7 ± 3.9	$t(84) = 1.99$ $p = 0.058$	$F_{2,273} = 1.911$ $p = 0.150$, $\eta^2 = 0.01$
Waist circum (cm)	92.5 ± 11.1	92.2 ± 11.3	$t(95) = 1.99$ $p = 0.551$	91.7 ± 10.7	91.2 ± 11.1	$t(93) = 1.99$ $p = 0.342$	91.9 ± 10.6	92.0 ± 12.0	$t(83) = 1.99$ $p = 0.847$	$F_{2,271} = 0.343$ $p = 0.710$, $\eta^2 = 0.003$
Daily physical activity (steps/day)	9604 ± 3256	9562 ± 3403	$t(93) = 1.99$ $p = 0.877$	9737 ± 2859	9761 ± 2907	$t(88) = 1.99$ $p = 0.941$	9661 ± 3923	9524 ± 3560	$t(79) = 1.99$ $p = 0.681$	$F_{2,260} = 0.066$ $p = 0.936$, $\eta^2 = 0.0005$

Table 2 Brain structure volumes (mean ± SD) at the four timepoints for each group: HRT, heavy resistance training; MIT, moderate intensity training; CON, non-exercising control group

	HRT				MIT				CON					
	Baseline	**1-year**	**2-year**	**4-year**	**Baseline**	**1-year**	**2-year**	**4-year**	**Baseline**	**1-year**	**2-year**	**4-year**	**F (group x time)**	**F (time)**
Total grey matter (mm^3)	595,868 ± 48,110	594,011 ± 47,916	591,175 ± 47,960	586,520 ± 48,126	593,738 ± 50,042	591,094 ± 50,003	588,288 ± 49,242	584,237 ± 49,570	588,597 ± 39,059	585,462 ± 38,357	582,880 ± 38,642	577,523 ± 36,883	$F_{6,819} = 0.816$, $p = 0.557$, $\eta^2 = 0.006$	$F_{3,819} = 231.549$, $p < 0.001$, $\eta^2 = 0.46$
Hippocampus (mm^3)	7641.6 ± 790.8	7592.0 ± 786.1	7532.6 ± 778.3	7426.1 ± 768.8	7533.7 ± 745.4	7490.2 ± 729.1	7433.0 ± 729.5	7297.5 ± 739.2	7432.2 ± 626.0	7358.5 ± 645.6	7313.5 ± 658.1	7171.7 ± 669.3	$F_{6,819} = 1.21$, $p = 0.299$, $\eta^2 = 0.009$	$F_{3,819} = 310.07$, $p < 0.001$, $\eta^2 = 0.53$
dlPFC (mm^3)	10,840.6 ± 1619.2	10,790.3 ± 1676.3	10,808.9 ± 1675.5	10,722.0 ± 1620.0	11,042.9 ± 1713.8	10,977.9 ± 1643.8	10,948.5 ± 1626.4	10,945.8 ± 1661.4	10,788.2 ± 1529.5	10,705.5 ± 1527.9	10,697.4 ± 1561.5	10,726.7 ± 1452.9	$F_{6,819} = 0.530$, $p = 0.786$, $\eta^2 = 0.004$	$F_{3,818} = 3.638$, $p = 0.013$, $\eta^2 = 0.01$
vlPFC (mm^3)	19,321.5 ± 2050.0	19,223.9 ± 2060.9	19,128.0 ± 2141.9	18,980.8 ± 2129.8	19,048.7 ± 2038.8	18,918.2 ± 2032.7	18,815.6 ± 2008.8	18,611.7 ± 1959.0	18,960.4 ± 1665.4	18,862.0 ± 1610.6	18,746.2 ± 1683.9	18,526.6 ± 1605.0	$F_{6,819} = 0.535$, $p = 0.782$, $\eta^2 = 0.004$	$F_{3,818} = 74.268$, $p < 0.001$, $\eta^2 = 0.21$
White matter hyperintensities (mm^3)	3621.4 ± 4873.3	3904.7 ± 5286.8	4194.0 ± 5578.3	4821.5 ± 6620.2	3360.1 ± 3225.0	3584.4 ± 3456.4	3738.2 ± 3623.4	4388.7 ± 4244.0	2814.2 ± 2311.6	3025.0 ± 2440.7	3357.9 ± 2946.0	4034.5 ± 3814.8	$F_{6,819} = 0.506$, $p = 0.804$, $\eta^2 = 0.004$	$F_{3,819} = 101.876$, $p < 0.001$, $\eta^2 = 0.27$

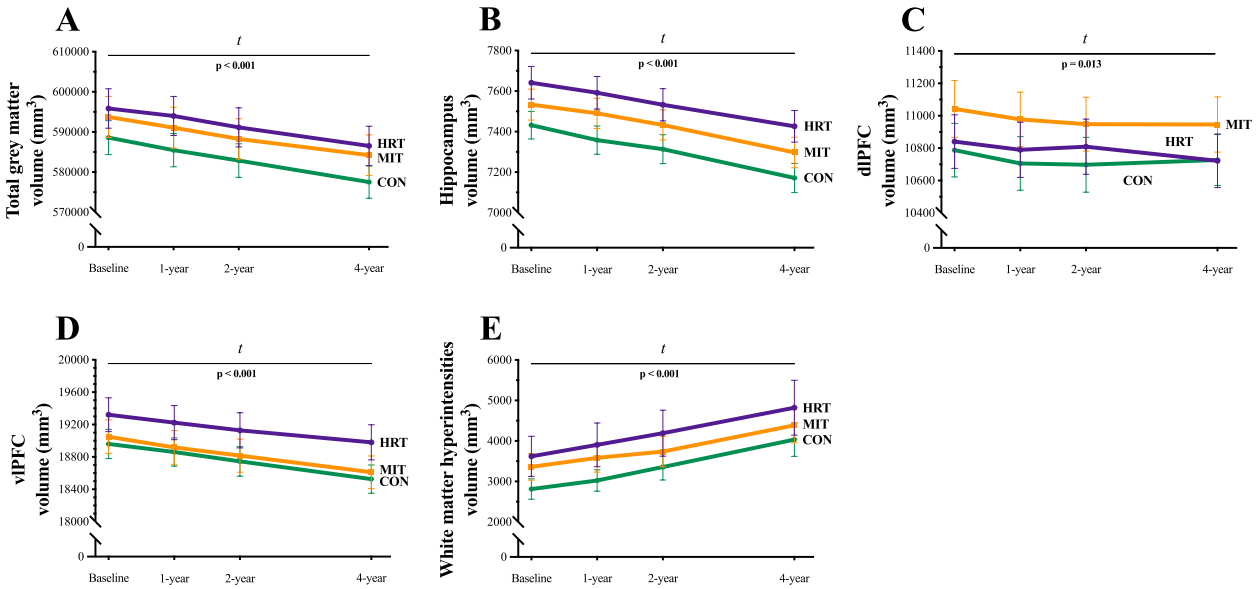

Fig. 2 Brain structure volumes (mean ± SEM) for baseline, 1-year, 2-year, and 4-year, across each group. **A** Total grey matter volume (mm^3) **B** Hippocampus volume (mm^3) **C** Dorsolateral prefrontal cortex volume (mm^3) **D** Ventrolateral prefrontal cortex volume (mm^3) **E** White matter hyperintensities volume ($mm.^3$). t, significant effect of time (A, B, D, E: $p < 0.001$; C: $p = 0.013$)

Other structural changes in the brain were not correlated with the change in strength.

Discussion

We found that one year of resistance training did not result in immediate or long-term (4 years) structural brain changes in older individuals around retirement age. Using the same MR scanner and protocol, repeated structural brain mapping showed that resistance training at neither heavy nor moderate loading influenced the pre-selected brain regions or vertex-wise analysis. Rather, each group displayed the expected decline for this specific age group [19, 37]. These results were thus in line with what has previously been shown for hippocampus volume [17, 18]. Further, there were no associations between change in leg muscle strength and change in volume of the pre-specified brain regions despite the fact that leg muscle strength was maintained from study start in the group of individuals who had performed the resistance training with heavy loads [26]. The progression of white matter hyperintensities, however, may be linked to muscular strength, as the change in volume was weakly associated with change in leg muscle strength.

There has been some evidence that brain structure may be associated with muscle function or structure [38], and there has been support of a long-term relationship between physical function and brain structure [39–41]. Here, we did not observe any resistance-training specific link to brain structural changes, and it remains unclear what, if any, the specific effects of resistance training would be on brain structure in aging. However, we did observe a small association between change in leg muscle strength and change in white matter hyperintensity volume. Considering that white matter hyperintensities are increasing with age [42], associated with many other negative health outcomes [43] and related to falls and impaired gait performance [42, 44], this association could be of potential relevance for older individuals. Aerobic exercise has shown to influence white matter structural integrity in older adults [41, 45], thus a potential influence from resistance training should be directly addressed in future studies.

The relationship between physical training and brain health in aging is complex, with some studies showing positive associations and some studies showing no effects [46]. One suggested mechanism for the crosstalk between muscle and brain is the release of myokines during exercise and the suggested existence of a muscle–brain endocrine loop [47]. One key myokine for brain plasticity is brain-derived neurotrophic factor (BDNF), which is produced by skeletal muscle during contraction [48]. Improvements in maximal oxygen consumption have been linked to increased levels of BDNF and hippocampus volume change [24]. With resistance training BDNF levels, as well as other myokines, should be increased, which so far has been observed in some intervention studies (mostly low- to moderate-intensity and short-term training), with the idea that finding the optimal exercise prescription for myokine expression is the key question for brain plasticity [49–51]. Unfortunately,

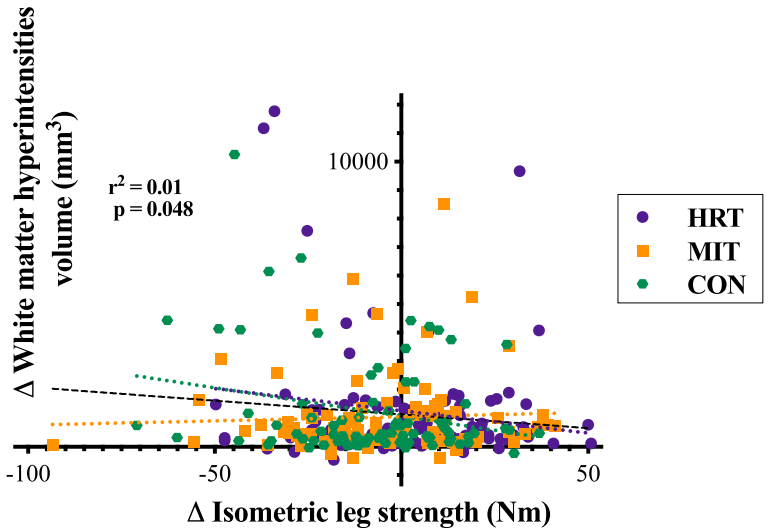

Fig. 3 Association between Δ white matter hyperintensity volume (change from baseline to 4-year follow-up) and Δ isometric leg strength (change in leg muscle strength from baseline to 4-year follow-up in the dominant leg). HRT, heavy resistance training; MIT, moderate intensity training; CON, non-exercising control group. For each group, regression slopes are displayed with dotted lines in corresponding colors. The overall regression slope is displayed with a block dotted line

the present study did not have any measures of myokine expression, hence we do not know if the resistance training evoked the hypothesized release of plasticity-inducing myokines. A deeper mechanistical understanding is necessary to further understand if resistance training plays a key role in lifelong learning and neuroplasticity, and what the active ingredient then would be.

A limitation in the current study was that the included participants were relatively well functioning and active. Measures of handgrip strength, for example, which is widely considered a reliable measure of overall muscle strength and functional status, compared well to normative values from age-matched peers [52, 53]. Further, the participants also walked a high number of steps per day, which, when compared to quartile data of steps/day in somewhat similar populations, indicates that the LISA-participants indeed had had high daily physical activity levels [54, 55]. Thus, perhaps the relevant question would be whether adding more exercise in terms of resistance training to an already active population would further benefit brain health? A similar question was recently addressed in the Generation 100 exercise study performed in another Nordic country. Here, the long-term (5 years) trajectories of brain structure and white matter hyperintensity development did not either seem to be altered by two different training intensities [15, 56]. Rather, it was in the control situation, that the lowest atrophy rate of the hippocampus was observed, and not after high intensity training, which they had otherwise hypothesized [13]. Noteworthy, participants in the control group in the Generation 100 study were encouraged to follow the rather demanding national activity guidelines of at least 30 min of moderate intensity exercise almost every day [12]. Combined with the general physical activity level of nearly 10,000 steps/day that was observed for the LISA-participants, one could speculate that the level of physical activity was already too high to induce any further benefits, or to influence the small changes in brain grey matter structure observed in this age-span. However, it should be noted that we cannot exclude that resistance training may have some beneficial effects on other structural brain measures not analyzed here. Despite this, there are several strengths in the present study. First, with a large sample size the LISA-study has so far been the largest study of resistance training and brain structure in humans. Second, the drop-out rate was low, and third the participants were followed over several years.

Conclusions

In conclusion, we did not observe any influence of resistance training on brain grey matter volumes measured with MRI in older adults around retirement age. We observed a small association between changes in leg muscle strength and development of white matter hyperintensities. Considering the many negative influences white matter hyperintensities have for a person's health, this finding should be further investigated in future studies.

Abbreviations

BMI	Body mass index
HRT	Heavy resistance training
MIT	Moderate intensity training
CON	Non-exercising control group

DXA	Dual-energy x-ray absorptiometry
MRI	Magnetic resonance imaging
CSA	Cross-sectional area
ROI	Region of interest
dlPFC	Dorsolateral prefrontal cortex
vlPFC	Ventrolateral prefrontal cortex
BDNF	Brain-derived neurotrophic factor

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12877-025-05778-z.

Supplementary Material 1.

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Authors' contributions
MK and HRS conceptualized the study. MK and CJB supervised the project. MBI and ATG administered the project, performed the experiments, and collected the data. EG supervised the MRI data collection. MBI performed the statistical analysis of data and created the visuals. MBI, CJB, and ND made the initial interpretation of data. MBI wrote the original draft. All authors reviewed and edited the manuscript for scientific content. Prior to submission, all authors read and approved the final manuscript.

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Data availability
The datasets supporting the conclusions of this article are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
The study was approved by the regional ethics committee (Capital Region, Copenhagen, Denmark, No. H-3–2014-017) and complied with the Declaration of Helsinki. All participants gave written informed consent before participating and the trial was registered on clinicaltrials.gov (NCT02123641).

Consent for publication
Not applicable.

Competing interests
HRS has received honoraria as speaker and consultant from Lundbeck AS, Denmark, and as editor (Neuroimage Clinical) from Elsevier Publishers, Amsterdam, The Netherlands. He has received royalties as book editor from Springer Publishers, Stuttgart, Germany, Oxford University Press, Oxford, UK, and from Gyldendal Publishers, Copenhagen, Denmark.

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