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Fitness, Gray Matter Volume, and Executive Function in Cognitively Normal Older Adults: Cross-Sectional Findings From the AGUEDA Trial

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ABSTRACT

The aim of the study is to investigate the association of cardiorespiratory fitness (CRF) and muscular strength indicators with gray matter volume (GMV) and to study whether fitness-related regions of GMV are associated to executive function (EF) in cognitively normal older adults. Ninety-one cognitively normal older adults (71.69 ± 3.91 years; 57.14% females) participated in this study from the AGUEDA trial. CRF was measured by a 2-km walking test and a 6-min walking test. Muscular strength was measured by handgrip, biceps curl, squats, and isokinetic strength tests. T1-weigthed images were obtained through a magnetic resonance scan. GMV was determined by voxel-based morphometric analysis. Standardized EF tests were performed. CRF did not show any positive association with GMV. Handgrip strength was positively associated with GMV ($p < 0.001$) in nine regions (β from 0.6 to 0.8 and k from 106 to 1927) and knee extension strength in three regions (β from 0.4 to 0.5 and k from 76 to 2776). Squats strength was negatively associated with GMV ($p < 0.001$) in two regions ($\beta = -0.3$, $k = 1102$ and $k = 152$) and the 2-km walking test in one region ($\beta = -0.4$, $k = 99$). Only handgrip strength-related GMV was associated with cognitive flexibility ($p = 0.039$, $\beta = 0.215$) and spatial working memory ($p < 0.03$, β 0.247–0.317), but not with EF score ($p > 0.05$). Muscular strength, but no CRF, may be positively related to GMV in cortical and subcortical regions, with implications for specific cognitive domains rather than the overall EF score. Specifically, handgrip strength was the indicator most associated with higher GMV, while squats strength and CRF were negatively related to GMV.

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1 | Introduction

Dementia is in the spotlight of health and social care systems in the 21st century. About 55 million people suffer from dementia worldwide as of 2019, and the prevalence is expected to increase three times by 2050 due to an expected increase in the number of adults over the age of 65 in the next decades [1]. Alzheimer disease (AD) is the most common case of dementia, characterized by progressive cognitive, functional, and behavioral deterioration which increases disability and dependency. AD patients have less cerebral gray matter volume (GMV) in frontal, temporal, and occipital regions, as well as hippocampal regions [2]. GMV atrophy is a marker of neurodegeneration and is associated with poorer cognitive performance, which increases with age [3]. Cognitive aging is a natural process that occurs across the lifespan. However, the extent and pattern of changes of the brain can vary among individuals. In this context, there is a need to identify protective factors during aging prior to the onset of the disease. Among different health-related factors, fitness might be a key component to healthy brain and cognitive aging [4].

Two of the main fitness components are cardiorespiratory fitness (CRF) and muscular strength. In particular, CRF is the most studied fitness component in relation to brain structure in elderly population [5–9]. Previous findings have indicated that CRF is associated with various aspects of cognition as well as markers of neuroplasticity in brain regions such as prefrontal cortex, hippocampus, and associated networks that overlap with the regions identified as showing the most rapid age-related losses in volume [10]. Indeed, older adults with higher CRF levels exhibit larger hippocampal volumes, and in turn, better memory performance [11]. However, there is a paucity of evidence for the role of other fitness components with GMV in older adults, such as muscular strength.

Recent evidence has pointed to muscular strength as an emerging marker of brain and cognitive health [12]. For example, high handgrip strength has been recently recognized as a potential indicator to determine the onset and progression of cognitive impairment [13, 14]. Despite the relevance of muscular strength for AD progression, only few studies have examined associations between muscular strength and GMV in cognitively normal older adults across different age ranges in the spectrum [15–19]. That is, two studies ($n = 247$ and $n = 387$ of community-dwelling older adults, respectively) using squats strength revealed positive associations with GMV in the cerebellum, caudate nucleus, putamen, postcentral gyrus, and superior parietal lobule [17, 18]. However, another study ($n = 217$ healthy older individuals) found that higher handgrip strength was associated with greater GMV solely in the left cerebellum and primary cortex [15]. Further, another study with a larger sample size ($n = 694$) found no association between handgrip strength and GMV [16]. Collectively, the aforementioned studies either focused on total or regional GMV [15, 19] or employed a whole-brain analytical approach [17, 18] within various elderly populations. In addition, from the different types of muscular strength (i.e., upper- and lower-body strength), all the studies focused only on one indicator, which often differed across studies. Therefore, we lack an understanding of how different muscular strength indicators relate to GMV, independently of CRF, due to considerable variability in how both muscular strength and brain outcomes have been measured. Such ambiguity in the literature has implications for our understanding of the role of muscular strength on neurocognitive health.

Executive function (EF) is typically defined as higher order cognitive processes that enable forethought and goal-directed action [20]. This aspect of cognition gradually declines during aging, affecting quality of life and general health. Fitness may slow age-related changes in EF and lower the risk of developing neurodegenerative disorders such as AD [21]. Understanding the association of different fitness components with brain structure, and further, how possible fitness-related brain associations relate to EF is important for developing public health strategies to improve the health and wellbeing of elderly adults worldwide. To the best of our knowledge, no previous study has examined the independent association of CRF and muscular strength with GMV and EF outcomes. Thus, this study aims (i) to investigate the association of CRF and several muscular strength measures with GMV using a whole-brain analytical approach and (ii) to study whether any brain regions related to fitness were associated with EF in a sample of cognitively normal older adults. We hypothesized that (i) CRF and muscular strength are independently associated with GMV in distinctive brain regions and (ii) fitness-related regions are related to EF.

2 | Materials and Methods

2.1 | Design and Ethics

Ninety-one cognitively normal older adults participated in this cross-sectional analysis of baseline data from the "Active Gains in brain Using Exercise During Aging" (AGUEDA) trial (ClinicalTrials.gov Identifier: NCT05186090; Submission date: December 22, 2021). Our sample size is highly characterized as we employed comprehensive fitness assessments as the lab- and field-based measures for both upper and lower body, MRI measurements for GMV, and the implementation of a whole-brain analytical approach. Detailed information about the AGUEDA project and sample and inclusion and exclusion criteria can be found elsewhere [22, 23]. In brief, participants were defined as (i) cognitively normal according to the Spanish version of the modified Telephone Interview for Cognitive Status, the Montreal Cognitive Assessment, and the Mini Mental State Examination and (ii) physical inactive as assessed by self-reported questions about structured exercise and physical activity. Physical inactivity was defined as not participating in any resistance exercise programs in the last 6 months and accumulating < 600 METs/week of moderate-vigorous physical activity. All participants were medically cleared by a sports medicine physician, ensuring that they had no physical impairments and psychiatric or neurological conditions. For this cross-sectional analysis, baseline data collected between March 2021 and May 2022 were used.

This study was conducted according to the Declaration of Helsinki and has been approved by the Research Ethics Board of the Andalusian Health Service (CEIM/CEI Provincial de Granada; #2317-N-19) on May 25, 2020. All participants gave written informed consent after all study's details were explained to them.

2.2 | Fitness

Fitness was assessed using indicators of CRF, including the 2-km walking test and the 6-min walking test, as well as measures of muscular strength such as handgrip strength, biceps curl strength, squats strength, and isokinetic strength [24]. Detailed information on each test performed is in Data S1.

2.3 | Magnetic Resonance Imaging (MRI) Procedure

2.3.1 | Data Acquisition

A 3.0T Siemens Magnetom Prisma Fit scanner (Siemens Medical Solutions, Erlangen, Germany) with a 64-channel head coil was used for image acquisition. Magnetization-prepared rapid gradient-echo (MPRAGE) sequence was used to collect T1-weighted images. Participants were instructed to fix the gaze at a white cross in black background during acquisition. The acquisition parameters were as follow: repetition time (TR) = 2400 ms, echo time (TE) = 2.31 ms, inversion time (IT) = 1060 ms, field of view (FOV) = 256 mm, resolution = 0.8 × 0.8 × 0.8 mm, 224 slices, and a scan duration of 6 min and 38 s. Further information regarding quality control and processing steps of structural images can be found in Data S2.

2.4 | Executive Function

An EF score was created using confirmatory factor analysis (CFA). The EF score was a standardized composite sum of z scores for each cognitive indicator retained in the CFA: trail making test, dimensional change card sort test, digit symbol substitution test, and spatial working memory test. Detailed information about each cognitive indicator could be found in Data S3.

2.5 | Covariates

Age, sex assigned at birth, years of education, and body mass index (BMI) were included in analyses as covariates based on previous literature [19].

2.6 | Statistical Analysis

The characteristics of the study sample are presented as means and standard deviation (SD). Visual inspection of the histograms and p-values ($p \leq 0.05$) from the Kolmogorov–Smirnov test indicated normal distributions, except for handgrip strength. An additional Q–Q (quantile–quantile) plot was generated to determine normality, and it was determined that no transformation was needed. Pearson correlation analyses were performed to evaluate the association between fitness indicators and covariates (i.e., age, years of education, and BMI). Outliers (i.e., 4 SDs far from the mean) were only found in cognitive data and thus, winsorized by replacing them with the value just above. These analyses were performed using R studio for Mac Version 2023.03.1 + 446 (main packages: tidyverse, lm.beta).

First, associations of each CRF and muscular strength indicators with GMV were conducted using linear regression in the General Lineal Model approach implemented in SPM12. GMV was determined by voxel morphometric analysis. Each model was adjusted for age, sex, years of education, and BMI as covariates. The voxel-level alpha significance threshold of $p < 0.001$ (uncorrected) along with the appropriate cluster extends for controlling for multiple comparisons in each analysis. The cluster extent was calculated with AlphaSim using RESTplus (Resting-State fMRI Data Analysis Toolkit) toolbox (parameters: cluster connection radius = 5 mm, actual smoothness of the data after model estimation, and a GMV mask of 128 190 voxels), with a further Hayasaka correction applied to account for the nonisotropic smoothness of structural images and to correct the t value. Then, we extracted the eigenvalues from the peak coordinates of each significant cluster using SPM12 and calculated the standardized β values for the fitness–GMV association for comparative purposes. In addition, we tested the independent associations of muscular strength and CRF indicators with GMV, controlling for handgrip strength when CRF indicators were predictors and for the 2-km walking test when muscular strength indicators were predictors. Furthermore, exploratory analyses were conducted to assess the interactions between demographics (i.e., sex, age, years of education) and the fitness indicators in relation to GMV; no significant interactions were found (all $p > 0.10$), and therefore, all analyses were conducted for the entire sample.

Second, linear regression analyses were performed to examine the association between the extracted mean GMVs, previously associated with any fitness variable, and EF score adjusted for age, sex, and years of education. In addition, exploratory analyses were conducted to examine the association between those fitness-related GMV regions showing a trend toward a significant association with EF ($p < 0.20$) and the four cognitive indicators included in the EF score, adjusting for the same covariates. R studio was implemented to perform these analyses with a significance level set at $p < 0.05$. Those analyses conducted utilizing the EF score encompassed a cohort of 90 participants due to one participant being excluded from the analysis because of the missing data in one cognitive indicator.

3 | Results

3.1 | Descriptive Characteristics

The descriptive characteristics of the study sample are shown in Table S1. Briefly, the sample had a mean age of 71.69 ± 3.91 years and was 57.14% female. Males completed more years of education than females (14.10 vs. 9.75 years), and males were fitter than females on all tests.

3.2 | Pearson Correlations Between Fitness Indicators and Covariates

All fitness indicators showed a significant correlation with the covariates (all $p \leq 0.05$, $r = 0.25$ and 0.82) (Figure 1). Regarding the correlation between fitness indicators and covariates, age was negatively correlated with knee extension strength, 2-km walking time, and meters walked in 6 min ($p \leq 0.008$, $r = -0.33$

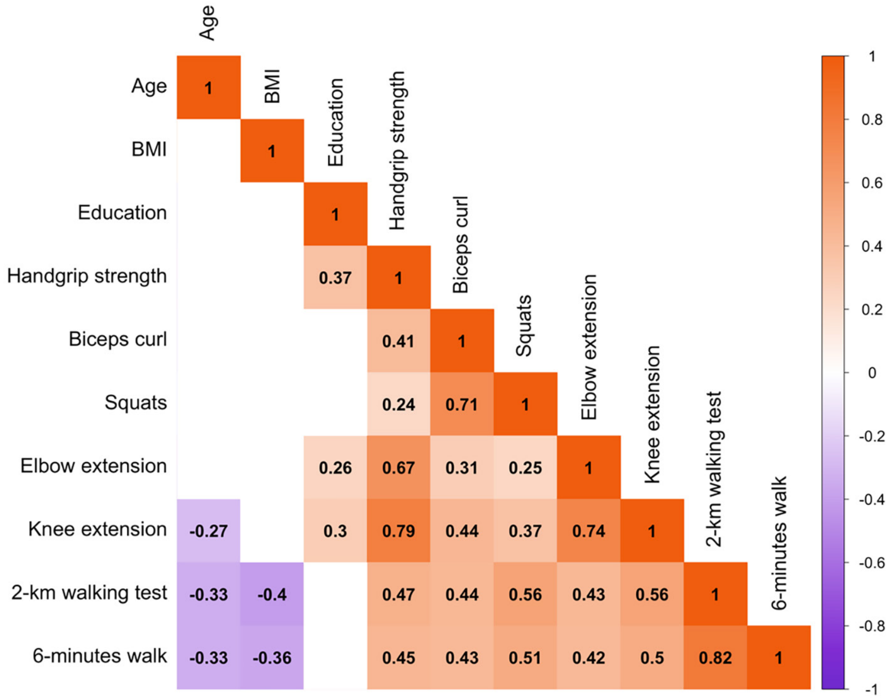

FIGURE 1 | Significant Pearson correlations between fitness indicators and covariates. BMI: Body mass index. Color bar represents the strength of the correlation as *r* values. The darker orange the color, the stronger the positive correlation between variables, and the darker purple the color, the stronger the negative correlation between variables. Blank spaces represent non – significant correlations. The fitness indicator 2-km walking test was reverted by multiplying it by −1 so that the higher value means better cardiorespiratory fitness.

and −0.27). BMI was negatively correlated with both CRF indicators ($p \leq 0.001$, $r = -0.4$ and -0.36). Years of education were positively correlated with handgrip strength, elbow extension strength, and knee extension strength ($p \leq 0.03$, $r = 0.26$ and 0.37).

3.3 | Association Between Fitness and GMV

Figure 2A (Table S2) presents brain regions showing positive associations between fitness and GMV in cognitively normal older adults, after adjusting by covariates. Handgrip strength was positively associated with GMV ($p < 0.001$) in nine clusters ($\beta = 0.6$–0.8 and $k = 106$–1927). Specifically, associations were observed in frontal regions (i.e., anterior orbital gyrus, triangular part of inferior frontal gyrus), parietal regions (i.e., middle part of cingulate gyrus, medial orbital gyrus), temporal regions (i.e., fusiform gyrus, lingual gyrus), subcortical regions (i.e., parahippocampal gyrus), cerebellum (i.e., cerebellum VI, cerebellum IV–V, cerebellum crus II), and insula cortex. Knee extension strength was positively associated with GMV ($p < 0.001$) in three clusters ($\beta = 0.4$–0.5 and $k = 76$–2776), specifically, in the lateral superior frontal gyrus and left and right cerebellum crus I. Biceps curl strength, squat strength, and elbow extension strength did not show any significant positive associations with GMV. Results were similar after adjusting for the 2-km walking test when muscular strength indicators were predictors (Table S4). There were no significant positive associations between any indicator of CRF and GMV ($p > 0.05$).

Figure 2B (Table S3) presents brain regions showing negative associations between fitness and GMV in cognitively normal older adults, after adjusting by potential covariates. None of the muscular strength indicators showed significant negative associations with GMV, with the sole exception of squats; squats strength was negatively associated with GMV ($p < 0.001$) in two clusters, thalamus and culmen ($\beta = -0.3$, $k = 1102$ and $k = 152$, respectively). In relation to CRF, better performance in the 2-km walking test was associated with lower GMV ($p < 0.001$) in the thalamus ($\beta = -0.4$, $k = 99$). No brain region showed significant negative association between meters walked in 6-min test performance and GMV. Results were similar after adjusting for handgrip strength when CRF indicators were predictors and for 2-km walking test when muscular strength indicators were predictors (Table S5).

3.4 | Association Between Fitness-Related GMV and Executive Function

The analysis did not reveal any significant associations between fitness-related GMV and EF ($\beta = -0.06$ to 0.17, $p = 0.095$–0.885). Fitness-related GMV regions showing a trend toward a significant association with EF ($p < 0.20$) were cingulate gyrus ($p = 0.072$), parahippocampus ($p = 0.124$), and cerebellum crus II ($p = 0.125$) (Table 1); thus, associations of those regions with individual cognitive indicators were further examined. Handgrip strength-related cingulate gyrus GMV and handgrip strength-related parahippocampal GMV showed positive significant association with spatial the working memory test ($p = 0.029$, $p = 0.009$, respectively), and handgrip strength–related cerebellum crus II GMV showed positive significant association with the dimensional change card sort test ($p = 0.039$). No other associations were revealed (all $p > 0.05$) (Table 2).

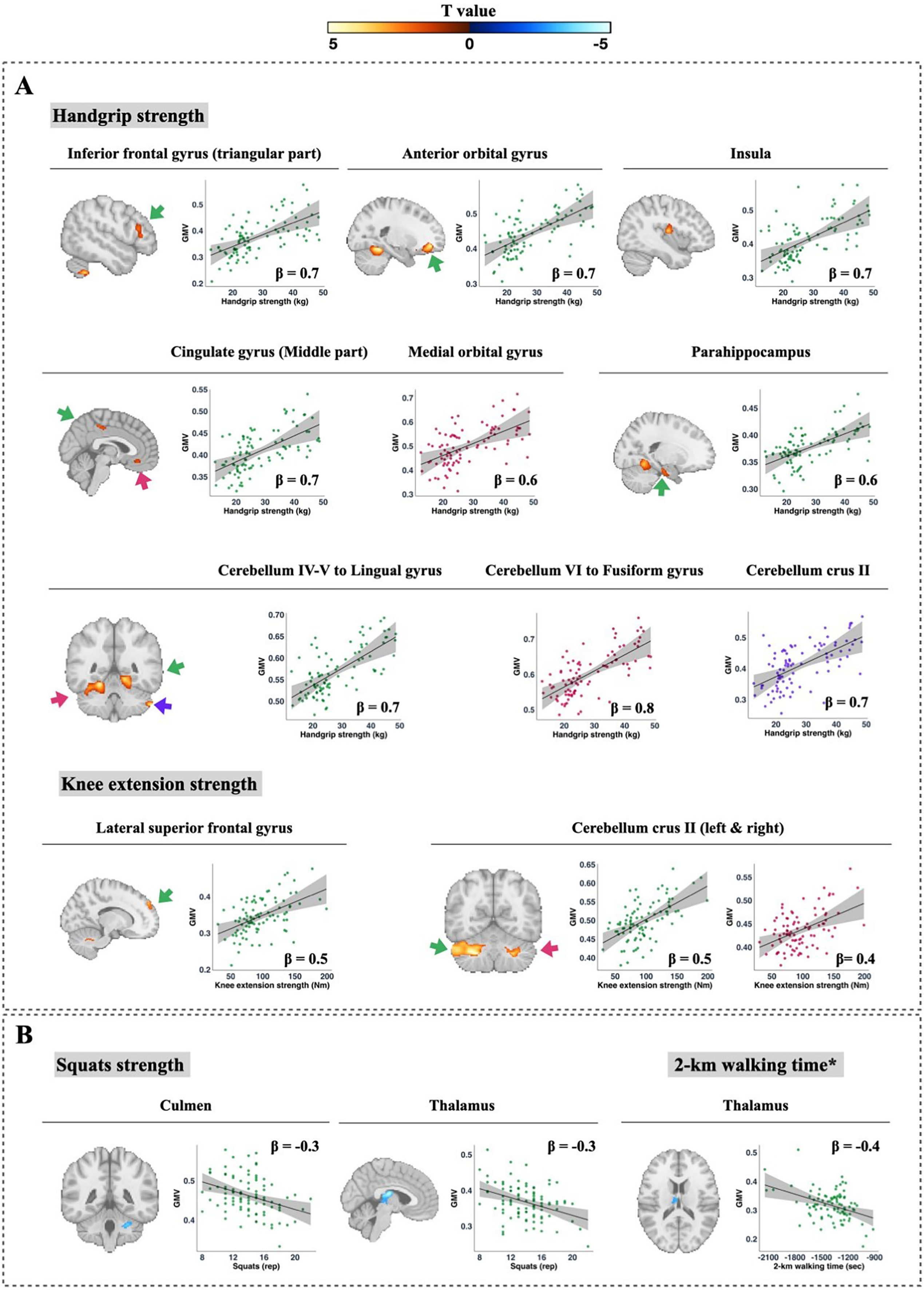

FIGURE 2 | Legend on next page.

FIGURE 2 | Brain regions showing positive (A) and negative (B) associations of fitness and GMV in cognitively normal older adults ($n=91$). Analyses were adjusted by age, sex, years of education, and body mass index. Maps were thresholded using AlphaSim at $p<0.001$ with $k=53$ voxels for the handgrip strength test, $k=55$ for the knee extension test, $k=41$ for squats test, and $k=50$ for the 2-km walking test, and surpassed Hayasaka correction (see Tables S2 and S3). The color bar represents *T*-values, with lighter orange color indicating higher significant positive association and lighter blue color indicating higher significant negative association. See Tables S2 and S3 for anatomical coordinates (X, Y, Z) given in Montreal Neurological Institute (MNI) Atlas space. Beta (β) presented is standardized. Scatter plots depict the relationship between fitness indicators and GMV in the associated brain region. Each point represents a participant in the study, with the *x*-axis representing the fitness indicator and the *y*-axis representing the GMV of the associated region. *The 2-km walking test was multiplied by −1 to interpret this indicator as "the higher, the better."

TABLE 1 | Association between fitness-related GMV and EF in cognitively normal older adults ($n=90$).

Test	Brain regions	β	p
Muscular strength			
Handgrip strength test (kg)	Inferior frontal gyrus (triangular part)	−0.032	0.734
	Cingulate gyrus (middle part)	0.176	0.072
	Medial orbital gyrus	0.121	0.212
	Anterior orbital gyrus	0.026	0.797
	Insula	0.045	0.642
	Parahippocampus	0.164	0.124
	Cerebellum IV, V to lingual gyrus	0.067	0.524
	Cerebellum VI to fusiform gyrus	0.115	0.260
	Cerebellum crus II	0.145	0.125
Squats (rep)	Thalamus	−0.046	0.645
	Culmen	0.059	0.562
Knee extension (Nm)	Lateral superior frontal gyrus	0.051	0.598
	Cerebellum crus I (left)	0.086	0.392
	Cerebellum crus I (right)	0.113	0.333
CRF			
2-km walking test (min)	Thalamus	−0.031	0.753

Note: Values are standardized regression coefficients (β). Analyses were adjusted by sex, age, and years of education.

TABLE 2 | Association between those fitness-related GMV regions showing a tendency to a significant association with EF ($p<0.20$) and cognitive indicators that make up the EF score in cognitively normal older adults ($n=90$).

Test	Brain regions	β	p	β	p	β	p	β	p
Muscular strength		**TMT**		**DSST**		**DCCS**		**SWM**	
Handgrip strength test (kg)	Cingulate gyrus (middle part)	0.117	0.269	0.062	0.511	0.104	0.341	0.247	**0.029**
	Parahippocampus	0.009	0.940	0.082	0.424	0.085	0.472	0.317	**0.009**
	Cerebellum crus II	0.027	0.791	0.091	0.316	0.215	**0.039**	0.106	0.347

Note: Values are standardized regression coefficients (β). Analyses were adjusted by sex, age, and years of education. Statistically significant values are shown in bold ($p<0.05$).
Abbreviations: DSST, digit symbol substitution test (total number of symbols correctly written); DCCS, dimensional change card sort test (inverse efficiency score of color trials); SWM, spatial working memory (inverse efficiency score of the mean of all conditions); TMT, Trail making test (execution time interference score (s)).

4 | Discussion

The main finding of the present study was that muscular strength, but no CRF, was positively associated with GMV in cortical and subcortical regions in cognitively normal older adults. In particular, handgrip strength was the indicator most associated with GMV in frontal, parietal, temporal, cerebellar, and subcortical regions. On the other hand, squats strength and

CRF (2-km walking test) were negatively related with GMV in the culmen (squats and CRF) and in the thalamus (CRF). In addition, fitness-related regions of GMV were not associated to EF score, but to specific domains (i.e., spatial working memory and cognitive flexibility). Taken together, these findings suggest that handgrip strength could be an important fitness marker associated with age-related cortical and subcortical neurodegeneration, with domain-specific cognitive implications rather than the overall EF score.

We examined the associations of muscular strength and CRF with GMV using a whole-brain analytical approach. Our results are partially consistent with the existent evidence in cognitively normal older adults [15, 17–19]. Previous studies found that muscular strength (measured by handgrip strength or squat strength) was positively associated with GMV across different brain regions, especially in the cerebellum, which is common to most of the studies [15, 17, 18]. However, our results revealed a negative association between squats strength and GMV, which is addressed below. Consistently, we also observed that handgrip strength and knee extension strength were positively associated with the larger clusters in the cerebellum, which plays a role in EF as well as global cognition, coordination, and motor learning [25]. Overall, handgrip strength was associated with the most brain regions, followed by knee extension strength. Importantly, these associations were maintained after controlling for CRF. This suggests that the observed relationships between muscular strength and GMV are independent of CRF, highlighting the robustness of our findings. Therefore, higher muscular strength during aging could have a protective impact on brain health, independent of CRF, in which handgrip strength appears to be the most robust indicator for predicting GMV across different brain regions in this population.

Several mechanisms have been suggested to understand our findings. Muscular strength is a predictor of sarcopenia, a syndrome characterized by a serious loss of skeletal muscle mass and strength [26]. Skeletal muscle acts as a secretory organ, releasing cytokines and peptides called myokines, which act as signaling agents facilitating communication between skeletal muscle and the brain [27]. Higher physical activity and lower sedentary time have been associated with greater muscular strength in older adults [28]. Indeed, prolonged periods of physical inactivity, which has been consistently associated with lower fitness/functioning capacity during aging [29], could result in a decline of muscular strength. This decline could disrupt the myokine response, and in turn, the muscle–brain crosstalk [30]. Another potential mechanism could be muscles' synthesis and secretion of insulin-like growth factor and brain-derived neurotrophic factor (BDNF) during exercise [31]. People with higher muscular strength have released more muscular BDNF acutely and chronically across their lifespan. Consequently, this secretion of BDNF could have helped to modulate brain plasticity. Thus, this is reflected in greater GMV in stronger cognitive normal older adults. This process also prevents neuronal decline and boosts hippocampal neuronal-neogenesis [32]. Hippocampal atrophy impairs communication with other cortical regions, resulting in a decline of cognitive function and motor control across different areas of the brain [33]. Therefore, it is plausible that older adults exhibiting higher handgrip strength may be facilitating the muscle–brain interface, consequently leading to a positive association with GMV within diverse cerebral regions.

Interestingly, there are several contrasting findings when comparing the associations between different muscular strength indicators and GMV in the present study. First, handgrip strength is related to more and distinctive brain regions than knee extension strength. Handgrip strength, an isometric strength indicator, is associated with the activation of multiple small muscles, leading to the recruitment of complex neural pathways and extensive cognitive processing [34, 35]. In contrast, knee extension strength (isotonic strength indicator) primarily engages the quadriceps, a larger muscle group, which might demand less fine motor control [36]. Furthermore, aging leads to a greater decline in lower limb muscle strength compared to the upper limbs, potentially due to a more sedentary lifestyle [37]. This might explain the distinctive brain regions associated with handgrip strength and knee extension strength. Second, knee extension strength was positively associated with GMV in superior frontal gyrus and bilateral cerebellum crus I, whereas squats strength was negatively associated with GMV in the thalamus and culmen. A possible explanation for this difference is that while both squats and knee extension measure lower body strength, the correlation between these indicators was weak ($r = 0.37$). Indeed, these measures were assessed using lab- and field-based tests, respectively, which may have different implications. Squats are a "daily" movement that we learn and perform throughout our lives, whereas knee extension is a more controlled movement and less common in daily activities. These differences may reflect that, in terms of GMV, these movements could have different impacts due to the nature of their execution. Lastly, each muscular strength indicator was related to distinctive brain regions, which may reflect not only the influence of stronger muscles but also the relevance of motor movements for each specific muscle–brain association. For example, Kapreli et al. [38] showed that different upper- and lower-limb movements exhibited different activation patterns in specific brain regions. Knee, ankle, and toes movements lead to a higher degree of involvement in the supplementary motor area proper, while finger movements lead to higher degree of involvement in contralateral primary sensorimotor cortex and ipsilateral cerebellum. Thus, depending on the muscle involved in each movement, this could lead to more complex and denser neural connections in some regions while less in other brain regions, potentially resulting in greater or lower GMV. These results suggest that the specific tests used to assess muscular strength, along with the particular movements and muscles involved, can influence the observed associations with brain volume, highlighting the importance of considering test-specific characteristics in research on physical fitness and brain health.

Contrary to some cross-sectional studies [5–7, 9], our results did not reveal any positive association between either of the CRF indicators (i.e., the 2-km walking time and the 6-min walking test) and GMV in cognitively normal older adults. This inconsistency with a large literature showing results with CRF and GMV could be explained by sample characteristics, methodology of assessing CRF, and methodological differences in how volumetric analysis was performed across studies (most studies do not use the DARTEL approach). For instance, most of the studies finding positive associations with CRF, used the current gold standard method of VO_2max (maximum oxygen consumption capacity), obtained from a maximal graded exercise test [11]. While VO_2max can be typically estimated from the CRF field-based tests with a moderate criterion-related validity (r=0.79 for the 2-km walking time and r=0.55 for the 6-min walking) [39], we were unable do so in our study due to concerns of wearing heart rate monitors during COVID-19 pandemic. This suggests that maximal exercise capacity, rather than submaximal capacity assessed by field-based tests (as used in this study), might be a more predictive measure of GMV. Thus, further studies examining the associations of CRF, assessed by both lab- and field-based tests, with GMV in cognitively normal older adults are needed.

Surprisingly, negative associations were revealed for one of the five muscular strength indicators (squats strength) and CRF (2-km walking time) with lower GMV in two brain regions, thalamus and culmen. These associations were independent of age, sex, years of education, BMI, and CRF (for squats) or muscular strength (for 2-km walking test). Both indicators, squats strength and 2-km walking time, were negatively related to GMV in the thalamus. One study also reported a reduction in thalamic volume in participants who underwent high-intensity interval training and moderate-intensity circuit training compared to a control group [40]. Given the thalamus's crucial role as a central hub for cortical connections and its links to subcortical regions [41], there may be compensatory mechanisms when the thalamus is functionally disconnected from certain regions while becoming hyperconnected with others [42]. Such alterations in thalamic connectivity could be reflected in GMV differences. However, additional investigation is needed to determine the underlying mechanisms and clinical significance of such relationship between better performance on squats and 2-km walking tests and lower GMV in the thalamus.

Despite associations between fitness and GMV across different brain regions, no associations were found between the fitness-related GMV regions and the EF score in our sample. Nevertheless, there was a trend for the associations of handgrip strength–related GMV in the cingulate gyrus, the parahippocampal, and the cerebellum crus II with the overall EF score. Upon exploratory examination of the association with each cognitive indicator of the EF score, we identified significant positive associations of GMV in those brain regions with the spatial working memory test and the dimensional change card sort test. CRF-related regions (i.e., prefrontal cortex and its subregions) have been previously related to EF processes such as inhibitory control or spatial working memory [6]. Of note, the previous study [6] limited its investigation to regions of interest that have demonstrated association with the cognitive processes they are focusing on which may explain the differences between results. Conversely, in our study, we used a whole-brain analytical approach; while this approach provides a comprehensive analysis without a priori hypothesis on specific regions, it may dilute specific brain–cognitive associations that could be detected using more targeted region-of-interest analyses. In addition, we computed an EF score encompassing various cognitive processes (i.e., cognitive flexibility, inhibitory control, working memory) [20], while the previous study used individual EF indicators, instead of an overall EF score. Indeed, we also found that fitness-related GMV seems to be more related to domain-specific EF processes (i.e., cognitive flexibility and spatial working memory) rather than to the overall EF score. Thus, future studies using whole-brain analytical approaches with larger sample size should examine the cognitive implications of the fitness–brain associations for both overall EF and domain-specific EF processes.

The present study has several strengths, including the integration of fitness measures such as different CRF and muscular strength tests to assess both upper- and lower-body strength in association with GMV. In addition, we employed a whole-brain analytical approach to further unravel how fitness relates to GMV without a priori region of interest established. The main limitations of the present study are the cross-sectional nature that does not allow us to draw causal inferences and determine the temporal direction of the associations. Thus, we cannot conclude whether changes in physical fitness precede or follow changes in brain measures. In this sense, future randomized controlled trials should investigate whether changes in physical fitness have benefits for GMV and EF in cognitively normal older adults. The use of field-based tests for assessing CRF without monitoring heart rate precludes the estimation of VO_2. Therefore, future research should aim to incorporate CRF field-based tests with heart rate monitoring and, when possible, complement these with gold standard measures such as maximal graded exercise test. The smaller sample size may affect the generalizability and robustness of our findings. Future studies with larger sample sizes including both CRF and muscular strength are necessary to confirm our results and further explore the relationship between fitness, GMV, and cognition in cognitively normal older adults. Lastly, while we have controlled for potential covariates, there may be other variables that could interfere with the revealed associations.

5 | Conclusions

Muscular strength, but not CRF, exhibited a positive relation to GMV in both cortical and subcortical regions among cognitively normal older adults. Specifically, handgrip strength was the indicator most related to a variety of brain regions, which, in turn, were linked to specific EF domains (i.e., spatial working memory and cognitive flexibility), but not to the overall EF score. However, other muscular and CRF indicators were either unrelated (biceps strength, elbow extension strength, and 6-min walking test) or negatively related (squats strength and 2-km walking test) to GMV. Future studies should investigate the link of muscular strength and CRF—assessed by both lab- and field-based tests—with GMV in cognitively normal older adults.

6 | Perspective

This study highlights the significant link between muscular strength and brain health among older adults, leveraging the muscle–brain crosstalk as a promising strategy to enhance specific cognitive domains in cognitively normal older adults. Handgrip strength emerges as a particularly reliable indicator of brain volume across various regions, aligning with previous research indicating its potential as a marker of brain health [15–17]. These findings advocate for considering muscular strength as a crucial element in future exercise intervention with the aim to counteract the age-related deterioration of physical functioning and cognitive and brain health.

Disclaimers

Detailed information regarding acknowledgments, funding and sponsor's role, conflicts of interest and author's and coauthors' contributions can be found in Data S4–S7, respectively.

Conflicts of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.