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Original Article

Association between structural changes in brain with muscle function in sarcopenic older women: the women's healthy ageing project (WHAP)

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Abstract

Objectives: The involvement of changes in brain structure in the pathophysiology of muscle loss (sarcopenia) with aging remains unclear. In this study, we investigated the associations between brain structure and muscle strength in a group of older women. We hypothesized that structural changes in brain could correlate with functional changes observed in sarcopenic older women. **Methods:** In 150 women (median age of 70 years) of the Women's Healthy Ageing Project (WHAP) Study, brain grey (total and cortex) volumes were calculated using magnetic resonance imaging (MRI) analyses. Grip strength and timed up and go (TUG) were measured. The brain volumes were compared between sarcopenic vs. non-sarcopenic subjects and women with previous falls vs. those without. **Results:** Based on handgrip strength and TUG results respectively, 27% and 15% of women were classified as sarcopenic; and only 5% were sarcopenic based on both criteria. At least one fall was experienced by 15% of participants. There was no difference in brain volumetric data between those with vs. without sarcopenia (p>0.24) or between women with falls (as a symptom of weakness or imbalance) vs. those without history of falls (p>0.25). **Conclusions:** Brain structure was not associated with functional changes or falls in this population of older women.

Keywords: Brain, Sarcopenia, Aging, Falls, MRI

Introduction

With the aging world population, the prevalence of sarcopenia – defined as muscle loss plus loss of strength and/or function[1] - and their common consequences, falls and fractures - is on the rise[2,3]. Aging-associated brain atrophy (including motor neurons and their neuronal pathways) and declined supra-spinal drive should lead to decreased nervous stimulation of muscles and their decline[4]. However, the association between structural changes in the brain and age-related muscle loss is not clear.

A large volume of research has been dedicated to investigating the relationship between brain white (WM) and grey matter (GM) volumes vs. muscular function and/or volume. In a comprehensive literature review by Kilgour et al,[5] the body of the evidence suggested weak association in either direction between white and grey matter mass and muscle mass/strength, however, no meta-analyses are available to statistically collate the studies.

Falls are associated with low hippocampus and putamen volumes in multiple sclerosis patients[6] as well as global brain atrophy in those with cognitive impairment[7]. However, there is limited information on whether sarcopenic subjects (that do not have any other disease condition), or those with increased risk of falls have different cerebral volumes.

The authors have no conflict of interest.

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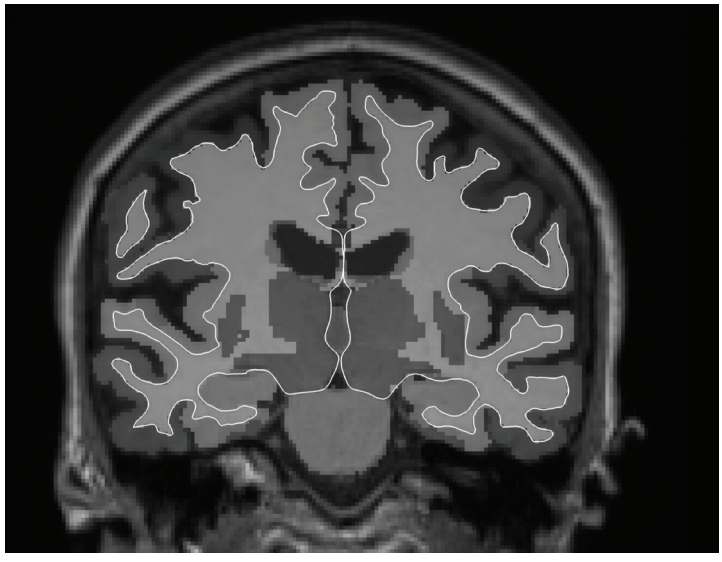

Figure 1. Example of T1 brain image of a 68-year old woman segmented using FreeSurfer software.

We studied the associations between muscle function and the cerebral volumes in both sarcopenic and non-sarcopenic participants of the Women's Healthy Ageing Project (WHAP) study. We aimed to determine whether there is a direct association between the size of brain's anatomical features with muscle performance and falls focusing on sarcopenic subjects.

Materials and methods

Study population

We used the data acquired from Women's Healthy Ageing Project (WHAP) - a longitudinal prospective study (since 1990) of Australian-born women[8,9]. Briefly, random selection and assessment of 2,001 women living in the Melbourne metropolitan area was conducted in 1990/91. Of the 779 women who met the entry criteria for the longitudinal follow-up (aged 45–55 years, menstruating, having a uterus and at least one ovary and not taking hormone therapy) 438 agreed to be seen annually across the menopausal transition from 1992 to 1999. In 2012, n=150 consented to undergo cerebral magnetic resonance imaging (MRI), whose falls history, physical activity and performance results were available were included in the current study[8]. This study was approved by the University of Melbourne Human Research Ethics Committee (HREC approval numbers: 931149X (92–99), 010528 and 010411 (02–09), 1034765 and 1339373 (since 2012).

MRI scans

MRI scans were performed using a Siemens 3T Tim Trio Scanner at Royal Melbourne Hospital (Melbourne, Australia) for volumetric MRI analysis. The protocol included high-

Table 1. Demographic characteristics; presented are median (IQR) or frequency (%).

Number of subjects who met inclusion criteria	150
Age (years)	70 (69, 73)
BMI (kg/m^2)	27 (24, 31)
Charlson comorbidity index = 0	130 (87%)
Charlson comorbidity index ≥ 0	20 (13%)
Current comorbidities	
Arthritis or rheumatism	83 (55%)
Cancer	3 (2%)
Diabetes	10 (7%)
Kidney disease	2 (1%)
Liver disease	3 (2%)
Osteoporosis	20 (13%)
Thyroid disease	19 (13%)
Transient ischemic attack (TIA)	6 (4%)
At least 1 fall within previous 6 months	23 (15%)
Handgrip strength (kg) (n=62)	23 (19, 26)
Timed up and go (s) (n=131)	8 (7, 10)
Calcium (mmol/L) (n=23)	2.4 (2.3, 2.5)
Creatinine (units) (n=119)	62 (57, 68)
Free T3 (pmol/L) (n=107)	4.8 (4.6, 5.1)
Free T4 (pmol/L) (n=107)	14.8 (13.6, 16.0)
TSH (mIU/L) (n=106)	1.9 (1.3, 2.9)

Table 2a. Comparison of cerebral volumes in sarcopenic vs non-sarcopenic subjects (based on grip strength results <20 kg, a cut off recommended by the first European consensus)[1]. Volumes are presented as median (IQR).

	Non-sarcopenic (n=45, 73%)	Sarcopenic (n=17, 27%)	*p*-value
Total cortical vol. (mm^3)	410427.3 (395085.9, 425124.1)	417364.91 (395097, 429814.5)	0.56
Left cortical vol. (mm^3)	203763.6 (196636.1, 213638.5)	208108.8 (197973.7, 214313.6)	0.55
Right cortical vol. (mm^3)	205903.3 (198449.9, 212306.7)	210865.1 (198186.7, 215501)	0.64
Cerebral grey matter vol. (mm^3)	418305.3 (395155.9, 448879.8)	409392.2 (385942.9, 452689.5)	0.86
Cerebral white matter vol. (mm^3)	567723.7 (542159.6, 578448.8)	566839.6 (531164.8, 585104.5)	0.97
Cerebral grey and white matter vol. (mm^3)	833107.6 (798225.9, 865892.4)	808866.9 (783625.0, 902531.6)	0.96
Left cerebellar grey mater vol. (mm^3)	49628.8 (47219.3, 52333)	48291.8 (47219.3, 51162.3)	0.31
Right cerebellar grey matter vol. (mm^3)	51472.7 (49146.7, 55029.3)	50312 (49113.9, 54508.4)	0.56
Cerebellar white matter vol. (mm^3)	30115.8 (28116.4, 31731.3)	28562 (27672.5, 31769.5)	0.33
Intracranial vol. (mm^3)	1419528 (1363359, 1502970)	1416596 (1345910, 1470001)	0.70

Table 2b. Comparison of cerebral volumes in sarcopenic vs non-sarcopenic subjects (based on grip strength results <16 kg, a cut off recommended by the revised European consensus)[16]. Volumes are presented as median (IQR).

	Non-sarcopenic (n=54, 87%)	Sarcopenic (n=8, 13%)	*p*-value
Total cortical vol. (mm^3)	412459.0 (398112.9, 425124.1)	399765.1 (370574.3, 433412.1)	0.49
Left cortical vol. (mm^3)	204985.2 (197884.8, 213638.5)	200435.0 (184646.7, 216145.2)	0.53
Right cortical vol. (mm^3)	207543.2 (199190.0, 212731.5)	199330.1 (185927.7, 217266.8)	0.41
Cerebral grey matter vol. (mm^3)	418076.0 (385942.9, 449561.2)	416507.1 (397643.1, 461171.5)	0.80
Cerebral white matter vol. (mm^3)	567319.2 (542159.6, 578494.6)	552106.6 (516566.8, 592086.6)	0.42
Cerebral grey and white matter vol. (mm^3)	833098.7 (796725.7, 869410.6)	816272.2 (768217.4, 909091.1)	0.83
Left cerebellar grey matter vol. (mm^3)	51153.5 (49113.9, 55002.7)	51898.9 (48378.9, 54732.8)	0.85
Right cerebellar grey matter vol. ($mm^3$3)	48629.6 (47189.2, 52184.0)	50315.1 (47936.8, 52196.4)	0.69
Cerebellar white matter vol. (mm^3)	30031.75 (28116.4, 32116.4)	27846.05 (27087.2, 30432.95)	0.15
Intracranial vol. (mm^3)	1418812.0 (1350522.0, 1502970.0)	1432605.5 (1348881.5, 1474382.5)	0.98

resolution T1-weighted Magnetization Prepared Rapid Gradient Echo (MPRAGE) MRI; isotropic 1 millimetres (mm) voxel (Repetition time (TR) = 2300 milliseconds (ms), Echo time (TE) = 2.98 ms, flip angle = 9°).

Image analysis

The high-resolution T1-weighted MPRAGE images were segmented by a validated image analysis software FreeSurfer (v. 5.3) (Figure 1), using established protocols[10-13]. The processing pipeline includes motion correction and averaging of the T1 weighted images, removal of any non-brain tissue using a hybrid watershed/surface deformation procedure, automated Talairach transformation, segmentation of the subcortical white matter and deep gray matter volumetric structures intensity normalization, tessellation of the gray matter-white matter boundary, automated topology correction and surface deformation following intensity gradients to optimally place the gray/white and gray/cerebrospinal fluid borders at the location where the greatest shift in intensity defines the transition to the other tissue class[10,12,13]. Maps were generated for: total cortical volumes, cerebral grey and white matter volumes, cerebellar grey and white matter volumes and intracranial volumes.

Physical performance and strength assessment

The Timed Up and Go (TUG) test[14] (the time required to rise from a seated position, walk 3 m from the chair, walk back to the chair and sit down again) was measured. Handgrip strength[15] was measured in the dominant hand using a hand dynamometer. Participants were asked to squeeze the dynamometer as hard as possible, with the average result of three trials being presented (in kilograms [kg]).

Sarcopenia

Appendicular lean mass and gait speed data were not collected in the WHAP study. As such, we defined sarcopenia using the handgrip data, with a cut-point of 16 kg for women used as recommended by the revised European Working Group on Sarcopenia in Older People

Table 3. Comparison of cerebral volumes in sarcopenic vs non-sarcopenic subjects (based on TUG test results >= 10.85). Volumes are presented as median (IQR).

	Non-sarcopenic (n=118, 90%)	Sarcopenic (n=13, 10%)	*p*-value
Total cortical vol. (mm^3)	410353.3 (393614.1, 424907.2)	404433.2 (353919.8, 437009.6)	0.62
Left cortical vol. (mm^3)	204386.7 (195954.6, 212694.5)	202896.3 (176015.1, 217976.9)	0.63
Right cortical vol. (mm^3)	205907.2 (197829.4, 212182.8)	201536.9 (177904.7, 219032.6)	0.63
Cerebral grey matter vol. (mm^3)	417531.9 (390050.2, 447812.5)	409392.2 (379403.1, 444152.7)	0.79
Cerebral white matter vol. (mm^3)	562819.1 (542159.6, 577238.8)	556236.2 (489210.8, 599068.6)	0.63
Cerebral grey and white matter vol. (mm^3)	829648.7 (790008.4, 868984.4)	804489.2 (732074.8, 902531.6)	0.63
Left cerebellar grey matter vol. (mm^3)	49446.0 (47189.2, 52527.0)	47397.8 (45225.3, 51063.3)	0.15
Right cerebellar grey matter vol. (mm^3)	51440.8 (49102.1, 54242.6)	50053.0 (47425.5, 54508.4)	0.47
Cerebellar white matter vol. (mm^3)	29603.15 (26966, 31731.3)	27925.8 (26324.8, 31769.5)	0.62
Intracranial vol. (mm^3)	1418510.5 (1358418.0, 1469177.0)	1418410.0 (1258891.0, 1478764.0)	0.85

Table 4. Brain volumetrics comparison between those with and without falls. Volumes are presented as median (IQR).

	Falls=0 (n=127)	Falls≥1 (n=23)	*p*-value
Total cortical vol. (mm^3)	413519.6 (393602, 427246.91)	404205.5 (393614.1, 423511.8)	0.27
Left cerebral cortical vol. (mm^3)	206126 (195556.3, 213921.5)	202896.3 (196106.2, 212407.1)	0.34
Right cerebral cortical vol. (mm^3)	207643.9 (197829.4, 214603.8)	201536.9 (195614.6, 212882.2)	0.25
Cerebral grey matter vol. (mm^3)	417648.4 (392254.5, 449561.2)	423622.1 (390050.2, 444152.7)	0.90
Cerebral white matter vol. (mm^3)	566914.8 (542159.6, 580777.6)	557464.2 (531164.8, 581579.8)	0.42
Cerebral grey and white matter vol. (mm^3)	832819.6 (790008.4, 873485.2)	828055.2 (783625.0, 857822.6)	0.58
Left cerebellum grey matter vol. (mm^3)	49491 (47160.3, 52511.8)	50272.2 (46874, 52902.5)	0.67
Right cerebellum grey matter vol. (mm^3)	51434.5 (48635.7, 54147.6)	50934.3 (49193, 56904.7)	0.43
Cerebellar white matter vol. (mm^3)	29675 (26919.1, 31877.9)	29063.5 (27373.2, 31935.9)	0.96
Intracranial vol. (mm3)	1421562(1357465, 1470001)	1399894 (1363972, 1478764)	0.99

(EWGSOP2)[16]. In the absence of gait speed, this study used the results of a TUG assessment to classify participants as having low physical performance/function. In this case, a cut-point of 10.85 seconds was used, which had been found to predict sarcopenia with a sensitivity and specificity of 66.7% and 88.7% respectively[17]. We did not use the TUG cut-off of EWGSOP2 (>20 s), not only because it was twice the value of the previously published literature[17], but also because its sensitivity and specificity are unknown. Instead we used 10.85 seconds as a cut-off with known sensitivity and specificity for sarcopenia[17].

Falls

Falls were defined as 'unexpected and involuntary loss of balance, causing the person an undesired contact with the ground'[18]. The occurrence of falls was assessed in a retrospectively asking the participant: 1) whether they had suffered a fall and, 2) the number of experienced falls during the six months prior to the assessment day.

Statistical analyses

Continuous variables are presented as median (interquartile range) and categorical as frequency (percentage). Rank sum test and Fisher's exact were used to investigate the differences between groups (sarcopenic vs non-sarcopenic and falls vs no falls). Multivariate analysis were not performed due to lack of associations. All analyses were performed using Stata 15.1 (StataCorp. 2017. Stata Statistical Software: Release 15. College Station, TX: Stata Corp LLC).

Results

Demographic characteristics are presented in Table 1. A total of 150 female participants were included in this study with the median age of 70 years.

TUG was performed in 131 participants with median result of 8.3 seconds and 10% of females had TUG ≥10.85 seconds (defined as sarcopenic)[17]. Handgrip strength was

measured in 62 participants (median handgrip strength 23 kg). Using handgrip criteria from EWGSOP2 definition (below 16 kg) resulted in 17 (27%) and 8 (13%) females classified as sarcopenic, respectively. TUG and handgrip strength were measured in 61 patients, of which 5 had sarcopenia. At least one fall was experienced by 23 participants (15%; in line with previously reported falls prevalence in urban dwelling older women)[19].

There was no evidence for an association between brain volume and sarcopenia (either defined using handgrip strength (Table 2a and 2b) or TUG (Table 3). Similar results were observed when comparing women with one or more falls within the last year (as a symptom of weakness or imbalance) and those without history of falls (Table 4).

Discussion

We did not find any associations between physical performance of the subjects or sarcopenia vs. cerebral volumes. Similarly, women with falls history did not have different cerebral volumes compared to those without falls history.

The results of previous studies exploring the association between the brain volume vs muscle function/volume are inconsistent[20-32]. In a large observational cohort study of over 400 people, Anstey et al. (2007)[21] found a relationship between grip strength and only the mid body area of corpus callosum, although this association was weak (r=0.103). In the same cohort Sachdev et al.[29] reported a similar association between brain atrophy and grip strength. However, Another study by Doi et al.[22] did not confirm these results.

The majority of studies that investigated the relationship between gait speed and brain volumes did not find any significant associations. Individual studies reported relationships between muscle strength with basal ganglia volume[33], white matter hyperintensities volume[26,34], brain stem lesions[27] and WM volume[35,36]. However, all correlations were weak with absolute values below 0.3. Also, longitudinally white matter hyperintensities burden was not associated with walking speed decline[5,34].

To our knowledge, the association between brain structure and muscle performance in sarcopenic patients with severe shortage in muscle strength vs those with normal muscle function has not been assessed previously. Sarcopenia is a disease status in which significant decline in muscle mass and strength occurs[1]; therefore, if changes in brain structure are related to muscle performance, they are more likely to be expected in sarcopenic subjects.

This is the first study that correlates brain structure with muscle performance and falls history in sarcopenic patients in a relevant population of older women. We used two criteria (grip strength and TUG test) to determine sarcopenia in addition to falls history, which is closely associated with sarcopenia. Both handgrip strength and TUG tests are valid diagnostics for sarcopenia, and both confirmed lack of associations between sarcopenia and changes in brain volumes in our population diagnosed using the most recent European criteria.

Nevertheless, the population was relatively young (mean age=70 y.o.), and the majority had normal grip strength and TUG and had not sustained multiple falls. Risk of falls significantly increases in those over 80[37], and being an age-associated condition[1], sarcopenia is predicted to increase in this population. Therefore, and considering the retrospective (falls) and cross-sectional (handgrip and TUG tests) nature of the study, follow up studies may reveal differences between those with and without sarcopenia. Nevertheless, it cannot be refuted that the lack of association between muscle function and brain volumes in our study could be partially due to limited sample size. We did not measure appendicular lean muscle mass; however, we used the accepted criterion for sarcopenia. The lack of concordance between handgrip, TUG and other diagnostic tests of sarcopenia is not exclusive to this study, and we have recently reported such lack of agreements in other populations[38]. We did not account for comorbidities like arthritides that may interfere the measurement of strength, however, employing tests that use both upper and lower limb strength (handgrip and TUG, respectively) decreases such a likelihood.

In conclusion, we did not find any association between brain structure and compartmental volumes with the physical performance in older women with or without sarcopenia, or those with and without falls. Future larger prospective studies are needed to confirm whether any associations are present and if they are of clinical relevance.

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