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Handgrip Strength Is Related to Hippocampal and Lobar Brain Volumes in a Cohort of Cognitively Impaired Older Adults with Confirmed Amyloid Burden

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Abstract.
Background: Strength and mobility are essential for activities of daily living. With aging, weaker handgrip strength, mobility, and asymmetry predict poorer cognition. We therefore sought to quantify the relationship between handgrip metrics and volumes quantified on brain magnetic resonance imaging (MRI).
Objective: To model the relationships between handgrip strength, mobility, and MRI volumetry.
Methods: We selected 38 participants with Alzheimer's disease dementia: biomarker evidence of amyloidosis and impaired cognition. Handgrip strength on dominant and non-dominant hands was measured with a hand dynamometer. Handgrip asymmetry was calculated. Two-minute walk test (2MWT) mobility evaluation was combined with handgrip strength to identify non-frail versus frail persons. Brain MRI volumes were quantified with Neuroreader. Multiple regression adjusting for age, sex, education, handedness, body mass index, and head size modeled handgrip strength, asymmetry and 2MWT with brain volumes. We modeled non-frail versus frail status relationships with brain structures by analysis of covariance.
Results: Higher non-dominant handgrip strength was associated with larger volumes in the hippocampus ($p = 0.02$). Dominant handgrip strength was related to higher frontal lobe volumes ($p = 0.02$). Higher 2MWT scores were associated with larger hippocampal ($p = 0.04$), frontal ($p = 0.01$), temporal ($p = 0.03$), parietal ($p = 0.009$), and occipital lobe ($p = 0.005$) volumes. Frailty was associated with reduced frontal, temporal, and parietal lobe volumes.

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Conclusion: Greater handgrip strength and mobility were related to larger hippocampal and lobar brain volumes. Interventions focused on improving handgrip strength and mobility may seek to include quantified brain volumes on MR imaging as endpoints.

Keywords: Brain volumes, handgrip, mobility, prevention

INTRODUCTION

Alzheimer's disease (AD) remains the most common cause of dementia [1] but is an increasingly recognized modifiable disorder with risk factors thought to prevent or delay up to 40%–50% of dementia cases [2, 3]. While efforts to discover effective drug treatments for AD continue [4], use of currently available prevention and risk reduction techniques are increasingly recognized as important given the decades of latency between appearance of AD pathology and earliest symptom progression [5]. Frailty, an age-related physiological decline in muscular strength and mobility, is one area of focus for modifiable risk because it has been noted to increase risk for dementia [6]. Asymmetry of muscular strength is also of interest in understanding these relationships as it can more sensitively predict frailty outcomes [7].

An increasingly utilized biomarker framework of AD pathology called ATN includes amyloid (A), tau (T), and neurodegeneration (N) as biomarkers that can be evaluated in living persons [8]. Amyloid and tau positron emission tomography (PET) [9, 10] along with cerebrospinal fluid [11] and more recently plasma biomarkers [12] are increasingly deployed in specialized clinical and research settings. For neurodegeneration, glucose metabolic imaging with FDG-PET [13] and volumetric quantification on magnetic resonance imaging (MRI) [14] are both accepted as clinical methods. Among these methods, MRI is the most accessible for patients while being less invasive and less costly compared to other techniques [15]. Brain MRI is also among the first line imaging methods in practice guidelines for dementia [16]. Characterization of brain atrophy in clinical practice has improved with the increasing availability of FDA-cleared software programs [17].

The ability to rapidly evaluate brain structure in individual participants on MRI provides an opportunity to study the influence of modifiable risk factors for dementia. Prior work showing lower brain volumes with obesity [18, 19], larger structural volumes with increasing physical activity [20, 21] and dietary choices [22] demonstrate that neuroimaging can track brain changes related to lifestyle.

Given the recent focus on AD prevention, the innovation of tools to evaluate brain structure and the increasingly recognized relationships between brain structure and modifiable AD risk factors, we sought to better understand these relationships. Specifically, we modeled the relationships between metrics of muscular strength with handgrip strength and asymmetry as well as mobility with the two-minute walk test (2MWT) in persons with amyloid biomarker evidence of AD as well as cognitive impairment and brain volumetric quantification with MRI. This was done as this category represents persons with confirmed AD pathology in whom risk factors and potential interventions be most specifically studies as opposed to persons in whom this information is not known and may have multiple or less specific etiologies of cognitive decline. We hypothesized that in this group, we can identify brain areas relevant for cognition that are influenced by these modifiable factors.

METHODS

Participants

All participants evaluated in this study were recruited as part of a larger study detailed in recent work [23]. Study approval was obtained from the WIRB-Copernicus Group Institutional Review board (WCG® IRB) (Protocol # 20190583) with informed consent obtained from each of the participants. Briefly, data from 38 individuals were evaluated at baseline at the Pacific Brain Health Center at Providence St. John's Health Center as part of a larger clinical trial were analyzed for this study. All individuals in the study prior to our data freeze were included. Screening of these individuals for the study for biomarker evidence AD [8] was done by either PET imaging with ^{18}F Florbetapir [24] or cerebrospinal fluid amyloid [11]. A global cognitive assessment was completed using the Montreal

Cognitive Assessment (MoCA) [25]. Handedness was obtained from participants by self-report.

Quantitative MR neuroimaging

Following screening for amyloid pathology, brain MRI scans were done at baseline on a 3T General Electric Scanner. Acquisitions included a T1 weighted spoiled gradient echo (SPGR) scan that underwent further volumetric quantification with Neuroreader [26], an FDA-cleared software program. The Neuroreader software produces raw volumes in mL, fraction of these volumes adjusted for total intracranial volume (TIV), a Z-score, and a Neuroreader Index which adjusts the Z-score for the sample size of the normal database from which the percentile comparison to that database is also derived. As we were interested in the generalized brain influence of handgrip strength, handgrip strength asymmetry, mobility, and non-frailty, we focused our assessment of brain structures on the broad representations of brain structures, namely lobar structures, and also a particular region of interest for AD, specifically the hippocampus.

Handgrip strength and mobility evaluation

Handgrip strength was measured using the NIH toolbox grip strength test [27]. This procedure entailed each participant squeezing a digital hand dynamometer while seated with both dominant and non-dominant hands at maximum pressure with each arm flexed at a 90-degree angle and positioned to the side based on instructions from a study examiner. This determines the amount of static force that the hand can squeeze around the dynamometer [28]. The examiner then records the force indicated on the dynamometer, measured in pounds in this study, in the NIH grip strength text toolbox program with related percentiles for dominant and non-dominant hands compared to reference data [29].

Participants also completed the 2MWT, which includes the number of meters a participant can walk in two minutes [30], as a measure of mobility. To determine if higher handgrip strength and increased mobility could additively relate to brain structure, a separate categorical variable was generated to define frail versus non-frail status of participants as follows: those who displayed both higher handgrip strength (dominant or non-dominant) and longer 2MWT results below their respective median splits were classified as frail; individuals scoring above or equal to these median splits were defined as non-frail. Since grip strength and two-minute walk test results are known to differ in women versus men [31, 32], we used sex-specific medians to determine frailty status.

Statistical analyses

Prior to analyses, data were inspected for outliers and homogeneity of variance to ensure appropriateness of parametric statistical tests. One outlier was identified for the parietal lobe analysis and excluded (Supplementary Figure 1B, red arrow). Demographic, strength, and mobility data were summarized for the full sample and compared between the frail and non-frail groups using Fisher's exact tests for categorical measures and *t*-tests for continuous variables. For each of the five brain regions investigated (hippocampus, frontal, temporal, parietal, and occipital lobes), separate multiple linear regression models were used to assess the relationship between handgrip strength (uncorrected scores for dominant and non-dominant hands) as well as mobility (2MWT, in meters and regional volumes). Temporal lobe measurement includes the hippocampus. An additional regression model examined handgrip asymmetry calculated using the following formula [33]:

Handgrip Asymmetry = [Dominant Handgrip Dynamometer Pressure – Nondominant Handgrip Dynamometer Pressure] / [Dominant Handgrip Dynamometer Pressure + Nondominant Handgrip Dynamometer Pressure]

Analysis of covariance was used to determine whether frail and non-frail participants differed in regional brain volumes. Effect size was determined with partial eta-squared estimates [34]. All models (regressions and ANCOVAs) adjusted for age, biological sex, years of education, handedness, body mass index, and TIV as these variables have been related to brain volumes in prior work [18, 35–37]. Given the novel nature of the study, we present complete results of all analyses. We used the Benjamini-Hochberg procedure (with a false discovery rate of 10%) to correct for multiple comparisons.

RESULTS

Table 1 details participant demographic for both frail and non-frail groups. As expected, the frail group had lower handgrip and 2MWT scores than the non-frail group.

Statistically significant associations (after correction for false discovery rate) were found between

Table 1
Participant demographics

Demographic variable*	Entire group $n = 38$	Frail group $n = 22$	Non-frail group $n = 16$	Statistics comparing frail and non-frail groups
Age	71.3 ± 7.4	70.2 ± 8.7	72.8 ± 5.0	t(36) = –1.1, $p = 0.3$
Biological Sex# (F/M)	(20/18)	(12/10)	(8/8)	$p = 1.0$
Years of Education	16.4 ± 2.4	15.9 ± 2.4	17.7 ± 2.3	t(36) = –1.5, $p = 0.1$
Handedness# (Right/Left/Ambidextrous)	(33/3/2)	(19/2/1)	(14/1/1)	$p = 1.0$
Body Mass Index	23.6 ± 3.4	23.7 ± 3.4	23.6 ± 3.5	t(36) = 0.1, $p = 0.9$
MoCA	21.9 ± 3.8	21.2 ± 3.8	22.9 ± 3.7	t(36) = –1.4, $p = 0.2$
Dominant Handgrip Strength (pounds)	93.0 ± 9.0	90.8 ± 9.1	96.1 ± 8.3	t(36) = –1.8, $p = 0.07$
Dominant Handgrip Percentile	41.6 ± 30.4	32.2 ± 30.5	53.3 ± 26.8	t(36) = –2.2, $p = 0.04$
Non-dominant Handgrip Strength	92.8 ± 9.4	90.8 ± 9.4	95.4 ± 9.0	t(36) = –1.5, $p = 0.1$
Non-dominant Handgrip Percentile	40.2 ± 30.3	31.8 ± 29.4	50.8 ± 29.0	t(36) = –1.9, $p = 0.06$
Handgrip Asymmetry	0.001 ± 0.02	0.00 ± 0.02	0.004 ± 0.02	t(36) = 0.5, $p = 0.6$
2MWT Score (meters)	156.6 ± 24.4	149.2 ± 23.7	166.8 ± 22.3	t(36) = –2.3, $p = 0.03$

*Numbers indicate mean + standard deviation (SD) for continuous measures. #Fisher's exact tests were used to compare categorical variables across groups.

Table 2
Association of handgrip strength and mobility to brain structures

Brain region	Dominant handgrip strength		Non-dominant handgrip strength		Handgrip asymmetry		Two-minute walk test	
	beta (SE)	p	beta (SE)	p	beta (SE)	p	beta (SE)	p
Hippocampus	0.01 (0.02)	0.5	0.06 (0.02)	**0.02**	–10.99 (6.38)	0.09	0.01 (0.00)	**0.04**
Frontal Lobes	2.14 (0.91)	**0.02**	1.23 (1.02)	0.23	380.27 (240.70)	0.12	0.64 (0.23)	**0.01**
Temporal Lobes	0.79 (0.52)	0.1	0.43 (0.56)	0.45	153.26 (134.21)	0.26	0.30 (0.13)	**0.03**
Parietal Lobes	1.01 (0.74)	0.2	0.43 (0.72)	0.55	122.30 (145.10)	0.40	0.39 (0.14)	**0.009**
Occipital Lobes	0.49 (0.29)	0.1	0.09 (0.32)	0.76	148.76 (71.63)	0.04	0.21 (0.07)	**0.005**

**All presented beta coefficients are unstandardized. Covariates: Age, biological sex, years of education, total intracranial volume, handedness, body mass index. Bolded p-values indicate statistical significance after Benjamini-Hochberg false discovery rate correction.

Table 3
Association of frailty with brain structures*

Brain Region (mL)	Frail group ($n = 22$)	Non-frail group ($n = 16$)	Statistics comparing frail and non-frail groups	Partial eta-squared
Hippocampus	6.61 ± 1.05	6.83 ± 1.21	F(1,29) = 0.6, $p = 0.5$	0.02
Frontal Lobes	307.01 ± 43.93	329.57 ± 41.62	F(1,29) = 5.2, $p =$ **0.03**	0.15
Temporal Lobes	173.09 ± 23.92	188.99 ± 26.87	F(1,29) = 6.0, $p =$ **0.02**	0.17
Parietal Lobes	160.77 ± 22.97	175.46 ± 23.48	F(1,29) = 5.7, $p =$ **0.02**	0.17
Occipital Lobes	79.93 ± 12.37	86.82 ± 15.96	F(1,29) = 3.1, $p = 0.09$	0.10

*F-statistics and partial eta-squared values presented are from ANCOVAs, controlling for age, biological sex, years of education, total intracranial volume, handedness, body mass index. Bolded p-values indicate statistical significance after Benjamini-Hochberg false discovery rate correction.

dominant handgrip strength and frontal lobe volume; non-dominant hand grip strength and hippocampal volume; and 2MWT and all 5 of the regional volumes we investigated (Table 2; Supplementary Figures 1 and 2). Further, frontal, temporal, and parietal lobe volumes were significantly greater in the non-frail group compared to the frail group (Table 3), partial eta-squared estimates indicating a medium to large effect size.

DISCUSSION

We found statistically significant relationships between handgrip strength, mobility, and hippocampal/lobar brain volumes in persons with both biomarker evidence of AD and cognitive impairment. In the dominant hand, the frontal lobes were larger with greater handgrip strength. Non-dominant handgrip strength related to larger hippocampal

volumes—a key target of AD pathology [38]. Additionally, a longer distance on the 2MWT was independently associated with all brain volumes investigated. Combining both handgrip strength and mobility to determine non-frail versus frail groups, frailty was associated with smaller frontal, temporal, and parietal volumes. Thus, higher measures of muscular strength and greater mobility related to larger brain volumes in regions relevant to memory and executive function. To the extent that handgrip strength and mobility are indicators of risk factors for dementia, these study results may lend insight into how frailty can modify such risk.

Handgrip strength is a measure of muscular function that can decline with aging as a consequence of sarcopenia [39], muscle loss that parallels aging and relates to immobility. Few studies have evaluated the relationship between this metric and volumetric quantification on MRI. One study of 1,284 participants in the Korean Genome and Epidemiology Study did not find a relationship between handgrip strength and total gray matter volume and parietal lobe gray matter [40]. This study did show a reduction in cognition in persons with sarcopenia defined by low muscle mass. Another study of 446 participants from the British birth cohort study found lower whole brain volume and lower score on matrix reasoning, a measure of non-verbal abstract reasoning, with lower grip strength [41]. A Freesurfer-based volumetric MRI study of 26 persons with lower grip strength and 26 matched healthy controls found lower volumes of hippocampal sub-regions right CA1, bilateral presubiculum, the left parasubiculum, left molecular layer, and left hippocampal amygdala transition area [42].

Handgrip strength may relate to dementia risk by representing underlying levels of inflammation. One study showed that greater handgrip strength related to a lower level of C-reactive protein that presents systemic inflammation [43], independent of age, sex, or body fat. Concurrently, inflammation including neuroinflammation is increasingly recognized as a potential mechanism in AD pathophysiology [44, 45]. Additionally, increased handgrip strength as midlife has been related to later life decreased white matter hyperintensities [41] suggesting that this metric may modify dementia risk though vascular risk factors such as hypertension. By contrast, there is comparative lack of evidence that handgrip strength is related to amyloid or tau deposition in the general population [46]. Thus, handgrip strength may represent a clinical metric to track as a proxy of underlying modulation of inflammatory states and related vascular risk factors for dementia.

In the current study, decreasing handgrip asymmetry predicted smaller occipital volumes did not survive correction for multiple comparisons. While handgrip asymmetry has not been specifically linked to brain volume in our study, it has been noted with different abnormalities in other work. For example, one study of 17,163 participants in the Health and Retirement study found that handgrip asymmetry was related to impaired performance on the Telephone Interview of Cognitive Status [7]. This relationship is believed to reflect the normal loss of hemispheric lateralization [47] with neurodegeneration.

Non-frail participants had higher MoCA test scores than frail individuals. Prior work has shown a relationship between handgrip strength and impaired cognition, also from the Health and Retirement study [48]. Another study replicated this finding with Mini-Mental State Examination results in Mexican-Americans [49]. Increased dementia risk has also been noted with declining handgrip strength. A systematic review and meta-analysis of 15 studies determined a higher hazard ratio both for cognitive decline (HR = 1.99) and risk for dementia (HR = 1.54) [50] and additionally specific risk of AD dementia for frail individuals.

The 2MWT is a measure of mobility and compliments strength in operationalizing frailty. However, no known studies have independently or in combination evaluated this metric against neuroimaging features. The 2MWT has been validated in persons with dementia and is not vulnerable to practice effects in that population [51]. A study of 145 heart failure patients showed a statistically significant relationship between 2MWT and the modified Mini-Mental State Examination as well as domain specific tests of executive function and language [52]. Another study showing a different test of walking speed in the Framingham Offspring study of 2,176 participants demonstrated a 2.5 fold higher risk of dementia in those with both a slow walking speed and weaker handgrip strength [53]. Thus, both sarcopenia and reduced mobility appear to modify dementia risk.

The main strength of this study was the selection of biomarker confirmed persons with AD pathology and impaired cognition. The MRI volumetric quantification method used in this study is also a strength as it has been validated technically [26], clinically [54, 55], and against other factors known to affect brain structure such as bilingualism [56]. Measurements of handgrip strength have not only been

shown to be reliable in the general population [57] but also in those with neurological disease [58], with a 0.7 or higher reliability coefficient. The combination of this metric with the 2MWT also highlighted additional areas related to brain structure, suggesting that both increased strength and mobility carry greater importance for brain structural volumes than either variable alone. The main limitation of the study is the cross-sectional design that precludes drawing causal relationships between handgrip strength and changes in brain structure. Further, we used a convenience sample of outpatients from our specialty memory clinic and the sample size was relatively small. Thus, future longitudinal analyses with a larger sample size will be important for better understanding the possible directions of causality between handgrip strength and progression of atrophy in AD. Additionally, future work can incorporate interrogations of different neuroimaging sequences such as perfusion MRI, diffusion connectome data, and neuroinflammation. Finally, future studies can combine these approaches in the evaluation of exercises designed to improved handgrip strength.

We have shown independent and additive relationships between muscular handgrip strength, mobility and MRI volumetric quantification of regional brain structures. Understanding modifiable risk factors for AD will require additional investigation of various aspects of such factors to determine how prevention and risk reduction measures may be optimally applied. It is possible that interventions specifically focused on improving ambulatory mobility and handgrip strength could be beneficial in improving dementia trajectories. Such work will continue to be important for optimizing cognitive health in those at risk for and suffering from AD.

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SUPPLEMENTARY MATERIAL

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