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Poorer Physical Fitness is Associated with Reduced Structural Brain Integrity in Heart Failure

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Abstract

Objective—Physical fitness is an important correlate of structural and functional integrity of the brain in healthy adults. In heart failure (HF) patients, poor physical fitness may contribute to cognitive dysfunction and we examined the unique contribution of physical fitness to brain structural integrity among patients with HF.

Methods—Sixty-nine HF patients performed the Modified Mini Mental State examination (3MS) and underwent brain magnetic resonance imaging. All participants completed the 2-minute step test (2MST), a brief measure of physical fitness. We examined the associations between cognitive performance, physical fitness, and three indices of global brain integrity: Total cortical gray matter volume, total white matter volume, and whole brain cortical thickness.

Results—Regression analyses adjusting for demographic characteristics, medical variables (e.g., left ventricular ejection fraction), and intracranial volume revealed reduced performance on the 2MST was associated with decreased gray matter volume and thinner cortex ($p < .05$). Follow up analyses showed that reduced gray matter volume and decreased cortical thickness were associated with poorer 3MS scores ($p < .05$).

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Conclusions—Poor physical fitness is common in HF and associated with reduced structural brain integrity. Prospective studies are needed to elucidate underlying mechanisms for the influence of physical fitness on brain health in HF.

Keywords

Brain; cognitive function; heart failure; neuroimaging; physical fitness

1. Introduction

Heart failure (HF) affects nearly six million Americans [1] and its prevalence will likely increase in coming years due to the increasing proportion of older adults and the high rates of conditions such as obesity, hypertension, and type 2 diabetes mellitus [2,3]. Patients with HF are at high risk for many adverse outcomes, including elevated mortality risk, recurrent hospital readmission, and reduced quality of life [1,4,5]. HF patients are also at risk for cognitive dysfunction and cognitive impairment is a major contributor to poor outcomes in this population [6,7]. Indeed, patients with HF are at risk for dementia (i.e., Alzheimer's disease, vascular dementia) [8,9] and as many as 75% of them exhibit impairment on neuropsychological tests of global cognition, attention, executive function, and memory [7,10,11].

White matter hyperintensities and gray matter atrophy are well documented in older adults with HF [11–16] and have been linked with reduced neuropsychological test performance [17]. Although the etiological underpinnings of structural brain changes in HF remain unclear, several contributing factors emerge from the extant literature. These putative contributors include advanced age [12], reduced left ventricular ejection fraction (LVEF) [12,16,19], depression and anxiety [16,17], and reduced cerebral perfusion [20,21], to name a few.

Another likely contributor to reduced brain integrity in HF is poor physical fitness. Reduced physical fitness is common in persons with HF [22] and it predicts poor outcomes [23–26]. Decreased physical fitness in HF patients is also associated with impairments in multiple cognitive domains [27–29]. In healthy elderly, reduced cognitive performance is associated with smaller regional brain volumes [30], and the association is moderated by concomitant vascular risk [31]. In healthy older adults, gross differences in cerebral morphology correlate with poor aerobic fitness [32–34]. Thus, it is highly plausible that cognitive impairments in HF may stem from deterioration in brain structure and poor physical conditioning. Extremely low levels of physical fitness in HF patients may result in reduced brain functioning and deterioration of brain structure, thus paving the way to persistent cognitive deficits.

Physical fitness provides many physiological benefits in cardiovascular disease populations [35], though its independent influence on brain structure in HF is unknown. The current study sought to determine whether physical fitness was associated with indicators of brain structural integrity in older adults with HF even after accounting for other factors linked to structural brain damage (e.g., HF severity). First, we investigated the effects of physical fitness on total cortical gray matter volume, white matter volume, and average cortical thickness. These indices were chosen because of the extant work highlighting the prevalence of atrophy and cortical thinning in cardiovascular disease and normal aging population with vascular risk factors [12,16,36,37]. We then examined the relationship between these MRI findings and global cognitive function to determine the possible impact of these structural brain differences on cognition.

2. Materials and Methods

2.1 Participants

The sample consisted of 69 consecutively enrolled persons with HF from an National Institutes of Health funded study examining neurocognitive function among HF patients. Strict inclusion/exclusion criteria were chosen for entry into the study to capture the independent contribution of HF on cognitive function. Specifically, the participants were between the ages of 50–85 years of age, native English speakers, and had an established diagnosis of New York Heart Association (NYHA) class II or III at the time of enrollment. Exclusion criteria included history of significant neurological disorder (e.g. dementia, stroke), head injury with more than 10-minutes loss of consciousness, severe psychiatric disorder (e.g. schizophrenia, bipolar disorder), history of substance abuse or dependence, renal failure, and sleep apnea. Participants were also excluded for any contraindications to magnetic resonance imaging (MRI) (e.g., pacemaker). Participants averaged 68.07 (SD = 8.02) years of age, 42.0% of them were women, and 84.0% Caucasian. Medical record review revealed that the current sample exhibited an average LVEF of 42.32 (SD = 14.11). Table 1 displays sample demographic and medical characteristics.

2.2 Measures

2.2.1 Neuroimaging—Whole-brain, high-resolution 3D T1-weighted images (Magnetization Prepared Rapid Gradient-Echo, MPRAGE) were acquired on a Siemens Symphony 1.5Tesla scanner for morphologic analysis. Twenty-six slices were acquired in the sagittal plane with a 230 × 100 mm field of view. The acquisition parameters were as follows: Echo time (TE) = 17, repetition time (TR) = 360, acquisition matrix = 256×100, slice thickness = 5 mm, and flip angle = 120°.

Morphological analysis of brain structure was completed with FreeSurfer Version 5.1 (http://surfer.nmr.mgh.harvard.edu). Detailed methodology for cortical thickness and regional and total volume derivation has been described in detail previously [38–41]. Briefly, FreeSurfer was used to preprocess images (e.g. intensity normalization, skull stripping) then provide an automated parcellation of cortical and subcortical structures via an automated processing stream. Freesurfer performs this parcellation by registering images to a probabilistic brain atlas, built from a manually labeled training set, and uses this probabilistic atlas to assign a neuroanatomical label to each voxel in an MRI volume. As part of the parcellation process, FreeSurfer derives cortical thickness measurements in various regions-of-interest (ROIs) throughout the brain. Parcellations were visually inspected for accuracy. For the purpose of this study, an average cortical thickness measurement was derived by taking the arithmetic mean of cortical thickness measurements from the component ROIs. Total gray matter, white matter, and intracranial volume measurements are derived automatically. Summary composites of volume and the mean of cortical thickness of each brain region including frontal, temporal, parietal, and occipital were also calculated using the organization schema as described in Desikan et al. (2006) [42].

2.2.2 Physical Fitness—Physical fitness was assessed with the 2MST [43]. The 2MST asks individuals to march in place for 2 minutes, lifting his/her knees to a marked target set on the wall set at the midpoint between the kneecap and crest of the iliac. The number of times the right knee met the marked target was counted. A greater step count within the time limit indicates greater physical fitness [43]. The average step count for women and men between the ages of 50–85 ranges from 71–115 and 60–107, respectively [43]. Poorer performance on 2MST has been previously linked with reduced cognitive function in HF populations [27].

2.2.3 Cognitive Function—The Modified Mini-Mental State Examination (3MS), a widely used brief cognitive screening tool, served as measure of the global cognitive function. The 3MS provides an estimate of global cognitive function, assessing aspects of attention, memory, language, and spatial abilities [44,45]. Lower scores on the 3MS indicate worse performance.

2.2.4 Depressive Symptoms—The BDI-II is a commonly used checklist that assesses depressive symptoms with strong psychometric properties in medical populations [46,47].

2.2.5 Demographic and Medical Characteristics—Participant demographic and medical characteristics were ascertained through self-report and corroborated through medical record review.

2.3 Procedures

The local Institutional Review Board (IRB) approved the study procedures and all participants provided written informed consent prior to study enrollment. A medical chart review was performed and participants completed demographic, medical and psychosocial self-report measures. Participants were then administered the 3MS to examine global cognitive function followed by the completion of the 2MST under the supervision of a trained research assistant. Finally, all HF patients underwent a brain MRI within two weeks of baseline assessment.

2.4 Statistical Analyses

A series of multiple linear hierarchical regression analyses examined whether performance on the 2MST was associated with total gray matter volume, total cortical white matter volume, and whole brain cortical thickness. For each analysis, medical and demographic characteristics were entered in block 1, including age, sex (1 = male; 2 = female), number of years of education, depressive symptoms (as assessed by the BDI-II), LVEF, diagnostic history of vascular risk factors, such as hypertension and diabetes (1 = positive diagnostic history; 0 = negative diagnostic history) and intracranial volume. The 2MST entered in block 2 to determine its independent effect on each imaging index. Follow-up partial correlations also examined the differential influence of 2MST performance on the frontal, temporal, parietal, and occipital brain regions.

Finally, follow up regression analyses controlling for the same demographic and medical characteristics were then conducted to determine the relationship between neuroimaging indices and cognitive function as measured by the 3MS.

3. Results

Physical Fitness and Cognitive Function

When compared to normative data accounting for age and gender, both men and women in this sample of HF patients exhibited low average physical fitness. Specifically, when using established cutoffs that suggest below average levels of physical fitness for males and females, 40.6% of the sample had a step count less than 60, and 60.9% of the sample had a step count less than 71.

Deficits in cognitive performance were also common as the sample averaged 92.96 (SD = 5.55) on the 3MS. Specifically, 20.3% of the sample scored below a 90 on the 3MS, 36.2% between 90 and 95, and 43.5% scored above a 95. See Table 2 for a descriptive summary of indicators of physical fitness and cognitive function. Partial correlations adjusting for demographic and medical characteristics revealed that poorer performance on the 2MST was associated with decreased scores on the 3MS ($r(60) = .30$, $p = .02$). Table 3 displays a partial correlation matrix adjusting for intracranial volume between key demographic variables (e.g., age, education, gender), brain structural indices, and physical fitness.

Physical Fitness and Neuroanatomical Measures

Demographic and medical characteristics were associated with total gray matter volume ($F(8, 60) = 6.42$, $p < .001$), total cortical white matter volume ($F(8, 60) = 6.14$, $p < .001$), and average cortical thickness ($F(8, 60) = 2.28$, $p = .03$). After accounting for intracranial volume and demographic and medical factors known to be associated with structural brain injury, reduced step count on the 2MST demonstrated incremental predictive validity for reduced total gray matter volume ($\beta = .38$, $p < .01$) and decreased whole brain cortical thickness ($\beta = .34$, $p = .01$). Figures 1 and 2 present an unadjusted scatter plot between the 2MST with total gray matter volume and whole brain cortical thickness. No such pattern emerged for total white matter volume ($p > .05$ for all). See Table 4.

Partial Correlations between Fitness and 3MS Performance with Specific Brain Regions

To identify possible differential effects of fitness on brain structure, partial correlations controlling for age, sex, number of years of education, BDI-II, LVEF, history of hypertension and diabetes and intracranial volume examined the association between physical fitness and specific brain lobes. Analyses showed that decreased step count was associated with reduced frontal ($r(59) = .39$, $p < .01$), temporal ($r(59) = .38$, $p < .01$), parietal ($r(59) = .42$, $p < .01$), and occipital lobe volume ($r(59) = .45$, $p < .01$). A similar pattern also emerged for cortical thickness of the frontal ($r(59) = .32$, $p = .01$), temporal ($r(59) = .36$, $p < .01$), parietal ($r(59) = .28$, $p = .03$), and occipital lobe ($r(59) = .23$, $p = .08$).

Neuroimaging and Cognitive Function

Follow up regression analyses also controlling for the same demographic and medical characteristics showed that reduced gray matter volume ($F(1, 59) = 3.04$, $\beta = .37$, $p = .01$) and decreased cortical thickness ($F(1, 59) = 2.76$, $\beta = .27$, $p = .04$) were associated with poorer 3MS scores. The 3MS was not associated with total white matter volume ($F(1, 59) = 2.22$, $\beta = -.14$, $p = .35$).

4. Discussion

Consistent with past work, reduced physical fitness was common and associated with lower cognitive function in this sample of HF patients. The current study extends these findings by showing that physical fitness is independently associated with brain morphology in HF patients. Several aspects of these findings warrant discussion.

Our findings suggest that poor physical fitness is associated with decreased gray matter volume and cortical thickness independent of the effects of HF severity and other medical and demographic characteristics. The observed association between poor physical fitness and reduced indicators of brain integrity is consistent with the extant evidence linking aerobic fitness with brain volume in patients with Alzheimer's disease and healthy adults [34,48–51]. There are several possible explanations for the unique relationship between physical fitness and brain structure. Better physical fitness may preserve cerebral structure through its beneficial effects on basic biological processes, including cell proliferation and survival [52], synaptic plasticity [53], neurogenesis [52], and protection against brain insult [54]. In addition, better fitness levels may lead to vascular benefits such as improved endothelial functioning and cerebral perfusion [55–61]. The effect of fitness on cerebral perfusion is noteworthy, as cerebral hypoperfusion and subsequent ischemia is believed to underlie neuropathological insult in HF patients [62,63]. Thus, increased fitness may attenuate vascular-related pathology such as white matter hyperintensities that also affect brain atrophy [64]. Because aerobic exercise increases cerebral blood volume [65], prospective studies should examine whether exercise-training programs might preserve brain integrity in HF patients by improving physical fitness levels.

Notably, the magnitude of differences was uniform across all cerebral lobes. Such pattern of a uniform decline is in contrast to a typical differential patter of cortical volume [66] and cortical thickness [67] reduction observed in normal elderly. It is, however, similar to the pattern of expansion of cortical shrinkage associated with vascular risk [68]. Viewed in conjunction with the global reduction in cerebral perfusion, this global pattern of structural decline appears characteristic of HF. A longitudinal study is needed to establish the temporal order of structural and hemodynamic changes in patients with HF.

In addition, the association between physical fitness and brain structure has implications for clinicians working with HF patients. An important aspect of the current study is the additional evidence for the role of physical activity and fitness levels in neurocognitive outcomes in persons with HF. Past work has shown that the structured exercise of cardiac rehabilitation improves cognitive function in persons with CVD [69] and future studies should examine whether similar benefits are found for HF patients. Cognitive impairment in HF is associated with reduced quality of life, poor treatment adherence, and increased mortality risk in HF [70,71] and it is possible that improved fitness levels may delay or even prevent some of these adverse outcomes in this high risk population.

Interestingly, LVEF was not associated with structural brain indices in the current study. Although past studies have also failed to show a linear association between LVEF and cognitive function [72], the exact reason for this lack of association is not entirely clear. One possible explanation may involve cerebral perfusion, as past work has failed to find a significant relationship between LVEF and cerebral blood flow suggesting that cardiac function may only partially account for cerebral hypoperfusion in HF patients [73]. Such findings may also help to explain the inconsistencies in the literature regarding the association between LVEF and cognitive test performance. It is possible that physical fitness level may prove to be a more promising assessment of neurocognitive outcomes than LVEF as it not only reflects the ability of the heart to deliver blood to the muscles, but is also associated with endothelial functioning, blood flow levels, among many others [22]. Future studies clarifying the relationship between systemic perfusion and neurocognitive outcomes are much needed.

The current findings also revealed a positive association between gray matter volume and cortical thickness with global cognitive function. Serber and colleagues (2008) [18] also showed that reduced neuropsychological test performance on measures assessing executive function predicted corresponding structural injury of the frontal cortex. Such findings suggest that cognitive impairment in HF is at least partly attributable to underlying abnormalities in brain morphology. The 3MS is a brief measure sensitive to cognitive impairment [44] and prospective studies should evaluate whether change in 3MS scores correspond with subsequent changes in brain morphology, particularly as these factors relate to physical fitness.

The current study is limited in several ways. First, our findings were based on cross-sectional data and prospective studies are needed to elucidate changes and contributors to brain structure over time in HF. The present study also assessed physical fitness using the 2MST, which offers several advantages, as it is brief and administered in the confines of the examination room. However, future studies should investigate the effect of physical fitness on brain structure in HF using more detailed measures of cardiorespiratory fitness, such as

VO2 max from stress testing. The current study controlled for prevalent comorbid conditions in HF that influence cognitive test performance and physical capacity in this population, though it is also possible that other comorbidities (e.g., respiratory disorders, medication effects) could have influenced performance on the 2MST. Prospective studies that account for such factors are needed to confirm the association between physical fitness and brain structure in HF. Future studies should also examine the association between cognitive test performance and brain morphology in HF patients using comprehensive neuropsychological test batteries. Similarly, future studies that compare fitness levels and brain morphology in HF vs. age-matched controls are needed to confirm the deleterious effects of poor fitness on neurocognitive outcomes in a HF population. Finally, fMRI studies are also needed to help clarify the effect of physical fitness on brain function, including regional examination, as specific brain structures (e.g., medial temporal lobe) have been shown to be particularly sensitive to the effects of exercise training and physical activity [74–76].

In summary, the current study found that reduced physical fitness was independently associated with brain structure among older adults with HF. These findings may offer as a possible explanation for the growing evidence linking poor fitness and cognitive function in persons with HF. Prospective studies are needed to elucidate the underlying mechanisms (i.e., cerebral perfusion) for the effects of physical fitness on brain health in HF.

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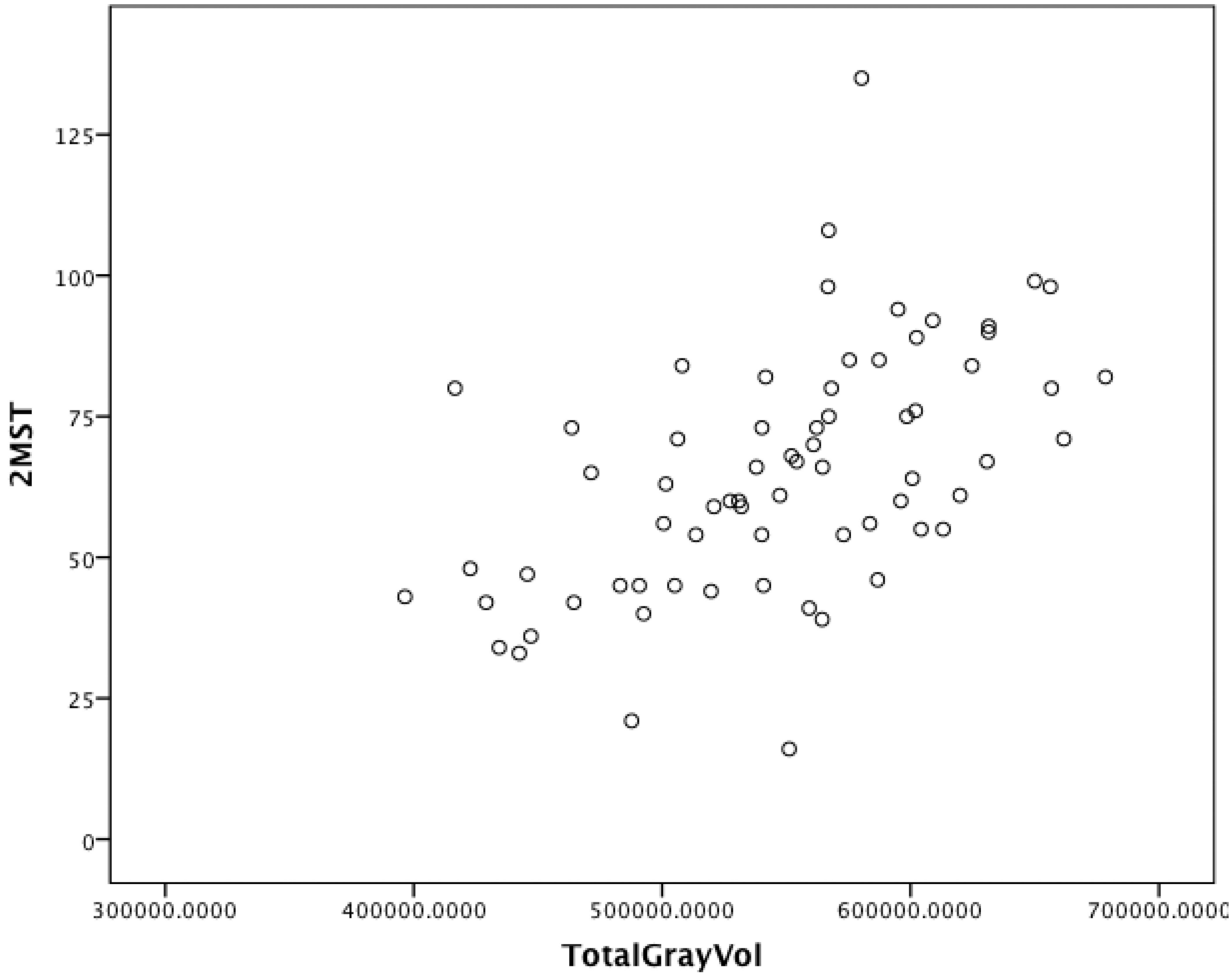

Figure 1.
Scatter Plot Examining the Association Between the 2MST and Total Gray Matter Volume in Heart Failure
Note. This graphical depiction does not adjust for key medical and demographic variables; 2MST = 2-Minute Step Test

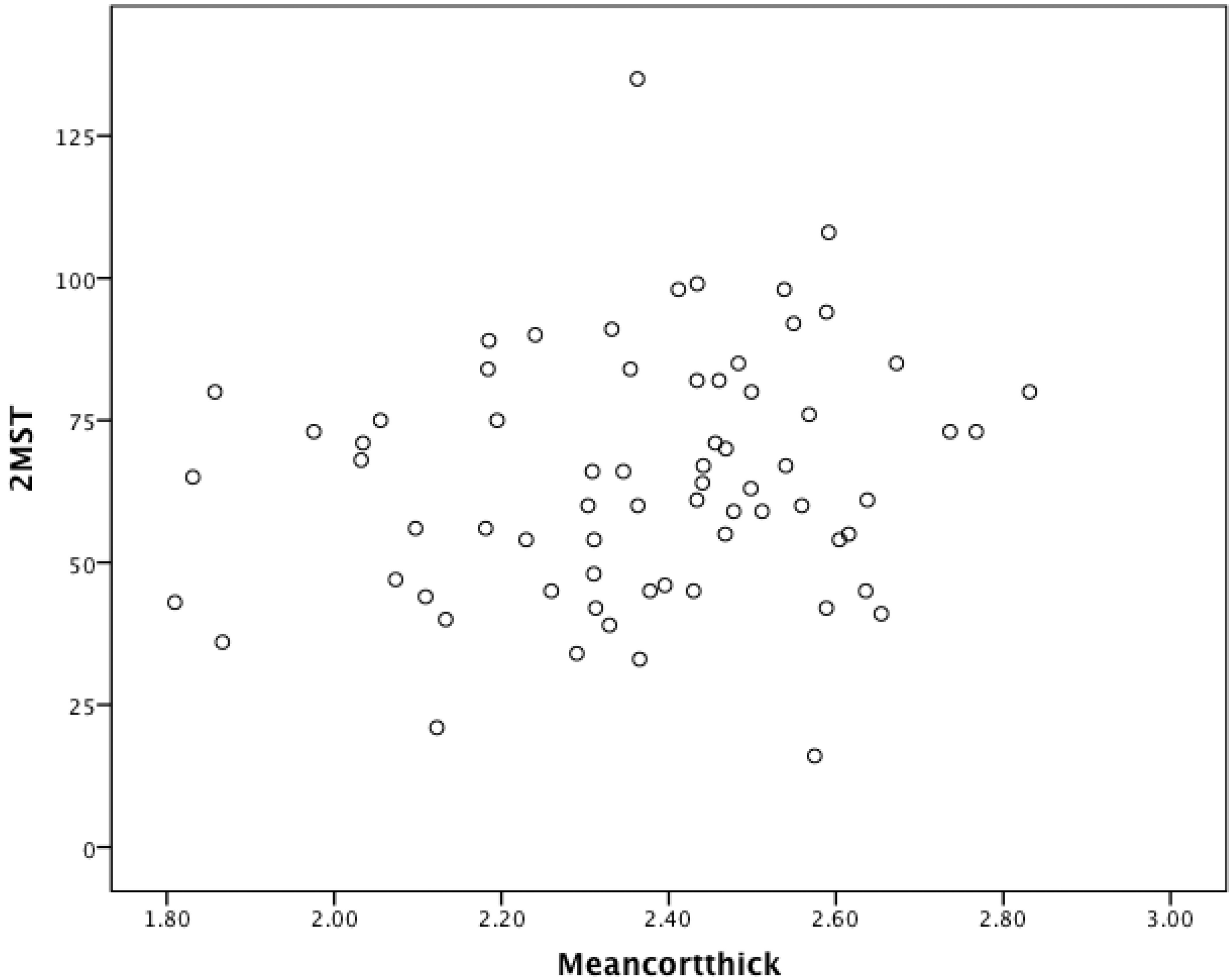

Figure 2.
Scatter Plot Examining the Association Between the 2MST and Whole Brain Cortical Thickness in Heart Failure

Note. This graphical depiction does not adjust for key medical and demographic variables; 2MST = 2-Minute Step Test; Meancortthick = Whole brain cortical thickness

Table 1

Demographic, Medical, and Cognitive Characteristics of 69 Older Adults with Heart Failure

Demographic Characteristics	
Age, mean (SD)	68.07(8.02)
Education, mean (SD)	13.83(2.73)
Female (%)	42.0
Race (% Caucasian)	84.0
Medical Characteristics	
BDI-II, mean (SD)	5.94(6.37)
LVEF, mean (SD)	42.32(14.11)
Diabetes (% yes)	29.0
Hypertension (% yes)	72.5

BDI-II = Beck Depression Inventory-II; LVEF = Left Ventricular Ejection Fraction

Table 2

Physical Fitness Levels, Cognitive Function, and Neuroimaging Characteristics of 69 Older Adults with Heart Failure

Physical Fitness, mean (SD)	
2-Minute Step Test Men	70.30 (22.17)
2-Minute Step Test Women	57.34 (18.37)
2-Minute Step Test Overall Sample	64.86 (21.50)
Neuroimaging, mean (SD)	
Gray Matter Volume	547653.90(65794.95) mm^3
Cortical White Matter Volume	513960.50(115118.86) mm^3
Cortical Thickness	2.36(.23) mm
Cognitive Function, mean (SD)	
3MS	92.96(5.55)

Note.

3MS = Modified Mini Mental State Examination

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Table 3

Partial Correlations Between Demographics, Physical Fitness, and Brain Structural Indexes (*N*= 69)

	EF	Age	Gender	Edu	2MST	GM	WM	Thick
EF	--	.09	.16	.11	.04	.14	− .03	.14
Age	--	--	.06	.00	− .24*	− .16	− .02	− .08
Gender	--	--	--	−.29	− .04	− .03	− .13	.18
Education	--	--	--	--	.30*	.12	.03	.10
2MST	--	--	--	--	--	.41*	− .14	.34*
Gray Matter	--	--	--	--	--	--	−.54*	.84*
White Matter	--	--	--	--	--	--	--	−.56*
Thickness								

Note.

EF = Ejection fraction; 2MST = 2-Minute Step Test; Edu = Education; 2MST = 2-Minute Step Test; GM = Gray Matter; WM = White Matter; Thick = Cortical Thickness

* $p < .05$

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Table 4

Physical Fitness Independently Predicts Brain Structure in Older Adults with Heart Failure (*N* = 69)

	Gray Matter	White Matter	Cortical Thickness
Variable	**β(*SE b*)**	**β (*SE b*)**	**β(*SE b*)**
Block 1			
Age	−.18(794.67)	−.01(1404.32)	−.13(.00)
Sex	.00(17783.29)	−.13(31426.13)	.28(.07)
Education	.03(2519.83)	.00(4452.98)	.10(.01)
LVEF	.12(456.81)	−.01(807.27)	.09(.00)
BDI-II	−.09(1049.91)	−.04(1855(.38)	−.17(.00)
Hypertension	− .12(14546.91)	.12(25706.90)	−.14(.06)
Diabetes	−.27(14317.61)*	−.06(25301.68)	−.16(.06)
Volume	.52(.05)*	.58(.09)*	−.20(.00)
R^2	.46	.45	.23
F	6.42*	6.14*	2 .28*
Block 2			
2MST	.38 (317.07)*	−.14(611.81)	.34(.00)*
R^2	.56	.46	.31
F for ΔR^2	13 .08*	1.46	6.95*

Note.

*denotes $p < 0.05$

Abbreviations: *β* – standardized regression coefficients, SE – standard error; LVEF = Left Ventricular Ejection Fraction; BDI-II = Beck Depression Inventory-II; Volume = Intracranial Volume; 2MST = 2-minute step test