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Daily Physical Activity Is Associated with Subcortical Brain Volume and Cognition in Heart Failure

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Abstract

Cognitive impairment in heart failure (HF) is believed to in part stem from structural brain alterations, including shrinkage of subcortical regions. Fortunately, neurocognitive dysfunction in HF can be mitigated by physical activity (PA), though mechanisms for this phenomenon are unclear. PA is protective against age-related cognitive decline that may involve improved structural integrity to brain regions sensitive to aging (e.g., subcortical structures). Yet, no study has examined the benefits of PA on the brain in HF and we sought to do so and clarify related cognitive implications. Fifty older adults with HF completed a neuropsychological battery and wore an accelerometer for 7 days. All participants underwent brain MRI. This study targeted subcortical brain volume given subcortical alterations are often observed in HF and the sensitivity of PA to subcortical structures in other patient populations. Participants averaged 4348.49 (SD = 2092.08) steps per day and greater daily steps predicted better attention/executive function, episodic memory, and language abilities, p's < .05. Medical and demographically adjusted regression analyses revealed higher daily steps per day predicted greater subcortical volume, with specific effects for the thalamus and ventral diencephalon, p's < .05. Greater subcortical volume was associated with better attention/executive function, p < .05. Higher daily PA was associated with increased subcortical brain volume and better cognition in older adults with HF. Longitudinal work is needed to clarify whether daily PA can attenuate brain atrophy in HF to reduce accelerated cognitive decline in this population. (*JINS*, 2015, *21*, 851–860)

Keywords: Physical activity, Heart failure, MRI, Brain volume, Cognitive function, Accelerometry

INTRODUCTION

Epidemiological evidence shows that heart failure (HF) is a risk factor for severe neurological conditions such as Alzheimer's disease (AD; Qiu et al., 2006). Milder forms of cognitive impairment can also be found in patients with HF, including in episodic memory and executive functions (Pressler et al., 2010). Longitudinal work in HF further demonstrates progressive worsening in these cognitive domains (Almeida et al., 2012; Alwerdt, Edwards, Athilingam, O'Connor, & Valdes, 2013; Hjelm et al., 2012; Van den Hurk et al., 2011). The etiology of cognitive impairment in HF is not entirely clear, although believed to involve structural brain alterations. Specifically, extant evidence shows that HF patients exhibit smaller gray matter volume in subcortical brain regions classically affected in aging and the early stages of AD, including atrophy of the medial temporal lobe and associated diencephalic network structures (Acosta-Cabronero & Nestor, 2014; Pan et al., 2013; Vogels et al., 2007; Woo, Kumar, Macey, Fonarow, & Harper, 2009).

Much attention has been dedicated to modifiable factors that may attenuate neurocognitive dysfunction in HF. Physical activity (PA) is the most common behavioral treatment prescription in HF that appears to represent one variable that may preserve cognitive functions in this population. For example, accelerometer-measured greater daily PA has been recently shown to predict better attention/executive function

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in HF and may even slow cognitive decline in this population (Alosco et al., 2015; Fulcher et al., 2014). Structured exercise programs (e.g., cardiac rehabilitation) have also been linked with cognitive gains in HF (Alosco et al., 2014). More broadly, greater daily PA is known to promote cognitive function and reduce risk for AD in older adults (Buchman et al., 2012; Kimura, Yasunage, & Wang, 2013), as well as mitigate cognitive impairment in patients with mild cognitive impairment and AD (Erickson, Weinstein, & Lopez, 2012; Farina, Tabet, & Rusted, 2014; Tanigawa et al., 2014).

Higher daily PA levels may lead to cognitive benefits in HF *via* increased volume of critical brain regions that modulate cognitive functions. PA may indeed promote structural brain integrity in HF *via* neurotrophic effects (e.g., neurogenesis and/or angiogenesis; Lee et al., 2014) and/or through various vascular benefits (e.g., increased cerebral perfusion). There is some support for the positive impact of PA on the brain (particularly subcortical structures). Past work has linked greater self-reported PA with better macro- and microstructural brain health in heterogeneous samples of patients with vascular disease (Gons et al., 2013; Kooistra et al., 2014). Moreover, in a sample of 299 adults from the Cardiovascular Health Cognition Study, greater self-reported walking activity predicted increased cortical lobar and subcortical (i.e., hippocampus, entorhinal cortex) volume 9 years later, which in-turn, reduced the risk for cognitive impairment by nearly two-fold (Erickson et al., 2010). Although the above findings are promising, they are limited by self-report assessments of PA. Nevertheless, recent work in neurological (i.e., mild cognitive impairment) and older adult samples demonstrates an association between objectively measured PA and brain volume, with specific effects for the hippocampus that was suggested to moderate PA-related memory benefits (Doi et al., 2015; Makizako et al., 2015; Varma, Chuang, Harris, Tan, & Carlson, 2015).

No study has examined the impact of PA on the brain in persons with HF and, more broadly, this phenomenon in cardiovascular disease populations is poorly understood due to limitations of past work (e.g., self-report assessment of PA). The purpose of the current study was to examine the associations among objectively measured PA, subcortical brain volume, and cognitive function in older adults with HF. This study targeted subcortical volume for two reasons: (1) the extant evidence for subcortical brain alterations in HF and the important role that these structures play in cognitive functions; and (2) past research that shows PA is strongly related to subcortical brain volume in neurological and older adult samples. Based on previous research, we hypothesized that higher levels of PA would be associated with larger subcortical volume, with specific effects for medial temporal lobe regions, as well as better cognitive test performance in domains such as executive function and episodic memory.

METHODS

Participants

The current sample consisted of 50 persons with HF that were recruited from a larger National Institutes of Health (NIH)-funded study that investigated modifiers of neurological outcomes in older adults with HF. Participants from the larger NIH study were stable patients with cardiac failure participating in routine cardiology care and were recruited *via* flyers and/or face-to-face methods from outpatient cardiology clinics at Summa Health System, a mid-sized Midwestern hospital. As part of the NIH-study protocol, a total of 92 participants underwent MRI, following completion of comprehensive cognitive testing, accelerometer assessment, and assessment of demographic and medical and clinical factors. The current sample consisted of participants that had complete data on all variables relevant to the present study and those with missing data were excluded listwise. As a result, the sample size of 92 was reduced to 50 after factors such as missing data, but primarily for invalid accelerometer data due to invalid wear and/or mechanical issues were accounted for. Those excluded were not significantly different from the current sample in terms of age, $t(90) = -0.22$, $p = .82$, sex, $\chi^2(df = 1, N = 92) = 0.22$, $p = .64$, HF severity, $t(87) = 0.80$, $p = .43$, or subcortical brain volume, $t(90) = -1.80$, $p = .08$.

Strict inclusion/exclusion criteria were used in the larger NIH-fund study that applied to the current sample. For inclusion, participants were between the ages of 50 and 85 years, English speaking, and had a diagnosis of New York Heart Association (NYHA) HF class II, III, or IV at the time of enrollment. Potential participants were excluded for a history or current diagnosis of a significant neurological disorder (e.g., dementia, stroke), head injury with ≥10 min loss of consciousness, severe psychiatric disorder (e.g., schizophrenia, bipolar disorder), substance abuse/dependence, and/or stage 5 chronic kidney disease. Participants were also not eligible for the current study if any MRI contraindications were present (e.g., pacemaker).

Measures

Physical activity

A GT1M accelerometer (Actigraph, Pensacola, FL) assessed PA over a 7-day period. Participants were instructed to place the accelerometer over the right hip, affixed to an elastic belt, and preferably worn under their waistbands. Daily step count was calculated by the accelerometer to provide a global indicator of overall PA in the sample. For the current population, a daily step count between 0 and 2499 represented sedentary, 2500 to 4999 as limited PA, and a >5000 daily step count was considered to be physically active (Tudor-Locke, Washington, & Hart, 2009). These cutoffs were used for descriptive purposes only. A valid day of wear was considered greater than or equal to 10 hr per day and the activity data were restricted to participants with at least 3 valid days of accelerometer wear. Average number of minutes per waking hours of the day spent in each activity level was calculated for each participant, as well as average minutes per day of accelerometer wear. On average, participants wore the accelerometer for 6.26 ($SD = 1.24$) days with a range of 3 to 7 days.

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Neuroimaging

Whole-brain, standard three-dimensional T1-weighted images were acquired on a Siemens Symphony 1.5 Tesla magnetic resonance imaging 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 = 17, repetition time = 360, acquisition matrix = 256 × 100, and slice thickness = 5 mm. Morphometric analysis of brain structure was completed with FreeSurfer Version 5.1 (http://surfer.nmr.mgh.harvard.edu). Detailed methods for volume derivation have been previously described (Fischl et al., 2002, 2004; Fischl, Sereno, & Dale, 1999). FreeSurfer was used to first perform image preprocessing (e.g., intensity normalization, skull stripping), and then to derive cortical and subcortical volume measures using the surface stream and the subcortical segmentation stream, respectively. FreeSurfer performs these parcellations by registering images to a probabilistic brain atlas, built from a manually labeled training set, and then using this atlas to assign a neuroanatomical label to each voxel in an MRI volume.

We performed several quality control post-processing procedures to ensure reliability and validity of brain tissue quantification. An initial reconstruction run was first conducted, followed by a manual and visual check/correction of the Talairach transform that was computed for each subject. The Talairach volume was fitted to match the target volume of the participant brain along the anterior/posterior commissures, temporal lobes, and midline. Each participant then underwent another reconstruction run. The quality of the skull strip was checked manually, along with segmentations, and the boundaries of the pial and white matter surfaces. This procedure was performed through the addition or deletion of voxels and using control points to re-negotiate the surface topology. A final reconstruction was then completed and re-checked to ensure all edits were factored in.

For the purposes of the current study, we examined subcortical brain volume (i.e., thalamus, caudate, hippocampus, amygdala, accumbens, ventral diencephalon, and substantia nigra), which was automatically derived with the subcortical processing stream (i.e., "aseg.stats"). Other subcortical structures of interest that were examined in this study due to their sensitivity to aging and PA included the parahippocampal gyrus and entorhinal cortex. For regional analyses, we calculated a total volume composite for each individual subcortical structure that consisted of the sum of the left and right hemispheres for each individual subcortical structure.

Cognitive function

A comprehensive neuropsychological test battery was administered to examine cognitive function in multiple cognitive domains, including attention/executive function, episodic memory, and language abilities. All measures used in this study are commonly implemented in routine clinical practice and their scores demonstrate excellent psychometric properties, including reliability and validity. The domains and measures assessed are presented below. Measures were assigned to their respective domain based on routine clinical neuropsychological operationalization (Lezak, 2004).

Attention/executive function

Trail Making Test A and B (Reitan, 1958), Digit Symbol Coding (Wechsler, 1997a), Letter Number Sequencing (Wechsler, 1997b), and the Frontal Assessment Battery (Dubois, Slachevsky, Litvan, & Pillon, 2000). For Trail Making Test, the dependent variable was seconds to completion, and Letter Number Sequencing was the number correct. For Frontal Assessment Battery, scores range from 0 to 18.

Episodic memory. California Verbal Learning Test-Second Edition (CVLT-II; Delis, Kramer, Kaplan, & Ober, 2000). Total number correct for total learning, short-delayed free recall, and long-delayed free recall served as the dependent variable.

Language. Animal Fluency test (Morris et al., 1989) and Boston Naming Test (Kaplan, Goodglass, & Weintraub, 1983). Number of animals named and total number correct on the Boston Naming Test represented the dependent variables.

Demographic and medical characteristics

A self-report medical history questionnaire ascertained participant demographic and medical characteristics. Medical record review then corroborated and supplemented participant self-report. Through these methods, diagnostic history of medical and clinical conditions was gathered to characterize the sample and statistically control for potential confounds. Participants underwent echocardiogram during their routine outpatient cardiology appointments to quantify left ventricular ejection fraction (LVEF) and medical record review ascertained LVEF of the sample. LVEF was included in the current analyses to account for the variance of intraindividual differences in HF disease severity.

Procedures

The Kent State University and Summa Health System Institutional Review Boards approved the study procedures and all participants provided written informed consent before study enrollment. All procedures were in compliance with Helsinki Declaration. During a single time assessment, height and weight were measured to calculate body mass index (BMI), and participants then completed demographic and medical history self-report measures, followed by the cognitive test battery to examine attention/executive function, episodic memory, and language. Participants then received an accelerometer and were instructed to wear the device each day for 7 days from the moment they wake until they go to sleep. All procedures were performed by a trained research assistant under the supervision of a licensed clinical neuropsychologist. At a separate study session, but within

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2-weeks of cognitive testing, participants underwent MRI that was conducted by a trained hospital-based MRI technician.

Statistical Analyses

All analyses were conducted in SPSS version 22 with a statistical significance level set at 0.05. For data reduction purposes and to reduce risk of type 1 error, composites were created for attention/executive function, episodic memory, and language that consisted of the mean of the raw scores of the measures that comprise their respective domains. To characterize the cognitive status of the sample, neuropsychological raw scores were also converted to *t* scores (normative mean of 50 and standard deviation of 10) using normative data (i.e., Halstead-Reitan and specific test developer norms). Consistent with clinical practice, a mean *t* score between 43 and 56 was considered average performance, and a *t* score <35 (i.e., 1.5 *SD* below the normative mean) was considered impaired.

Two-step hierarchical regression analyses were performed to examine the association between PA, cognitive function, and subcortical brain volume. We chose to perform a series of separate regression analyses in light of the flexibility of this approach to examine the association between independent and dependent variables while accounting for potential confounds; regression analyses also permit close of examination of effect sizes through multiple methods (e.g., beta's, R^2), which is critical for this study given the relatively modest sample size. Indeed, the current sample size of this study precluded the necessary power to perform model-based approaches that allow for simultaneous examination of variables such as structural equation modeling.

For cognitive function, a separate regression analysis was performed for each cognitive domain. Covariates were carefully selected to preserve statistical power given the relatively modest sample size and only variables well known to influence both PA and cognitive function were entered in block 1. We indeed sought to statistically control for key demographic and medical variables that are best known to affect neurocognitive outcomes, regardless of the study population, in light of the lack of a control and/or group. Specifically, block 1 included age, sex (1 = male; 0 = female), diagnostic history of depression (known to impact PA and cognition in this population, Garcia et al., 2011; Alosco, Spitznagel, Miller, et al., 2012; 1 = positive history; 0 = negative history), and LVEF. Daily step count was then entered in block 2 to determine its independent association with cognitive function for each domain.

The regression analyses were then repeated for total subcortical brain volume and regions of interest as the dependent variables; however, we also included intracranial volume (ICV) as a covariate to control for individual differences in head size. Statistical control for ICV is one of the most common and statistically flexible methods to account for intraindividual differences in head size (for a full review, see O'Brien et al., 2011). A final set of regressions then examined the relationship between subcortical volume and neuropsychological test performance.

RESULTS

Demographic and Medical Characteristics

See Table 1 for sample demographic and medical characteristics. The average age of the sample was 68.22 (*SD* = 9.32) and 38.0% were female. The current sample exhibited relatively mild levels of HF, as the mean LVEF was 43.22 (*SD* = 13.78) and only 32.0% of the sample exhibited an LVEF <40%. Medical comorbities such as hypertension and elevated total cholesterol were also common. Table 2 presents correlations between medical and demographic variables with PA and neurocognitive function.

Physical Activity Levels

Participants averaged 4348.49 (*SD* = 2092.08) steps per day. According to daily step count cutoffs, 24.0% of the sample were classified as sedentary, 40.0% as limited PA, and 36.0% were physically active. Bivariate correlations revealed no relationship between daily step count with medical or demographic variables (see Table 2).

Physical Activity Predicts Cognitive Function

Refer to Table 3 for a full description of cognitive test performance in the current sample. Relative to normative standards, examination of the mean *t* scores showed that participants generally fell in the average range with the exception of the Frontal Assessment Battery. Mean performance on this measure of frontal systems functioning fell in the low average range (mean *t* score of 41.95). However, cognitive impairment was still evident among participants. Specifically, participants exhibited a *t* score <1.5 *SD* below the mean on many measures of cognitive function particularly on tests of attention/executive function and episodic memory. Cognitive impairment was most commonly observed on the Frontal Assessment Battery, in which 32.0% of the sample exhibited a normative *t* score <35.

Table 1. Sample characteristics

Demographic variables	
Age, mean (*SD*), median, range	68.22 (9.32), 69.50, 50–83
Sex, % female	38.0
Race, % Caucasian	86.0
Clinical/medical variables	
Left ventricular ejection fraction, mean (*SD*), median, range	43.22 (13.78), 42.0, 15–75
New York Heart Association (% Class II, III, IV)	92.0, 6.0, 2.0
Body mass index, mean (*SD*), median kg/m^2, range	29.78 (6.56), 28.15, 19.19–46.15
Type 2 diabetes mellitus, % yes	22.0
Hypertension, % yes	66.0
Elevated total cholesterol, % yes	56.0
History of depression, % yes	20.0

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Table 2. Correlations among demographic/medical variables with physical activity and neurocognitive function

	Daily steps	Attention/ executive function	Memory	Language	Subcortical brain volume
Age	−0.04	−0.20	−0.34*	−0.31*	−0.10
Sex (1 = males; 0 = female)	0.14	−0.07	−0.30*	0.11	0.32*
LVEF	−0.08	−0.01	−0.08	−0.13	0.00
BMI	−0.27	−0.16	−0.13	−0.04	−0.14
Depression (1 = yes; 0 = no)	−0.12	−0.16	0.09	0.08	0.00
Type 2 diabetes mellitus (1 = yes; 0 = no)	−0.10	−0.21	0.06	0.00	−0.31*
Hypertension (1 = yes; 0 = no)	−0.24	−0.18	0.15	−0.05	0.00
Elevated total cholesterol (1 = yes; 0 = no)	0.08	0.04	0.08	−0.10	0.11

Note. $N = 50$ for all correlations.
*$p < .05$.
LVEF = left ventricular ejection fraction; BMI = body mass index.

Hierarchical regression analyses controlling for age, sex, LVEF, and diagnostic history of depression showed that daily step count predicted attention/executive function, $\beta = 0.31$, $p = .03$, language abilities, $\beta = 0.35$, $p = .01$, and episodic memory, $\beta = 0.27$, $p = .049$. Higher daily step count was associated with better cognitive function in each domain (Table 4).

Physical Activity and Subcortical Brain Volume

Regression analyses controlling for age, sex, LVEF, history of depression, and ICV revealed a significant association between daily steps per day and subcortical volume, $\beta = 0.30$, $p = .04$ (see Table 5). Greater daily steps per day predicted increased subcortical volume. Follow-up region of interest regression analyses were performed controlling for the identical covariates listed above. These analyses showed that steps per day emerged as a significant predictor of total volume of the thalamus, $F\Delta = 5.29$, $\Delta R^2 = 0.07$, $\beta = 0.27$, $p = .03$, and ventral diencephalon, $F\Delta = 4.32$, $\Delta R^2 = 0.05$, $\beta = 0.24$, $p = .04$. Daily step count was not associated with volume of any other regions of interest, including the caudate ($F\Delta = 0.01$; $\Delta R^2 = 0.00$; $\beta = -0.01$; $p = .91$), hippocampus ($F\Delta = 0.001$; $\Delta R^2 = 0.00$; $\beta = 0.01$; $p = .98$), amygdala ($F\Delta = 0.34$; $\Delta R^2 = 0.01$; $\beta = 0.08$; $p = .56$), parahippocampal gyrus ($F\Delta = 0.02$; $\Delta R^2 = 0.00$; $\beta = 0.02$; $p = .90$), or entorhinal cortex ($F\Delta = 0.29$; $\Delta R^2 = 0.00$; $\beta = 0.06$; $p = .59$).

Subcortical Volume and Cognitive Function

A final set of regression analyses explored the relationship between subcortical volume and cognitive function. Total subcortical volume predicted attention/executive function, $F\Delta = 5.81$, $\Delta R^2 = 0.09$, $\beta = 0.34$, $p = .02$, and there was a trend for language abilities, $F\Delta = 3.19$, $\Delta R^2 = 0.06$, $\beta = 0.27$, $p = .08$. In each case, greater subcortical volume was associated with better cognitive function. No such pattern emerged for episodic memory, $p = .69$. Larger thalamic ($r(43) = 0.29$; $p = .05$) and ventral diencephalic ($r(43) = 0.37$; $p = .01$) volume predicted better attention/executive function. Ventral diencephalon ($p = .09$) and the thalamus ($p = .18$) did not predict language abilities.

DISCUSSION

Consistent with past work, the current study suggests that daily PA is associated with higher test scores in multiple

Table 3. Cognitive test performance

	Mean (*SD*), raw scores	Range	Mean (*SD*), T-score	% T-Score <35
Attention/executive function				
Trail Making Test A, seconds	38.14 (12.72)	23–84	51.71 (9.06)	8.0
Trail Making Test B, seconds	112.30 (65.19)	35–301	45.45 (21.29)	12.0
Digit Symbol Coding	50.74 (13.40)	24–81	48.04 (8.47)	10.0
Letter Number Sequencing	9.50 (2.31)	4–14	53.50 (7.83)	0.0
Frontal Assessment Battery	15.68 (2.68)	9–18	41.95 (21.63)	32.0
Memory				
CVLT-II Total	40.54 (12.28)	0–69	49.66 (12.16)	6.0
CVLT-II SDFR	7.48 (3.51)	0–15	47.10 (12.17)	10.0
CVLT-II LDFR	8.14 (3.87)	0–16	47.40 (12.30)	14.0
Language				
Animal Fluency	19.32 (5.62)	11–34	53.83 (12.50)	2.0
Boston Naming Test	53.98 (6.13)	31–60	51.42 (12.23)	12.0

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Table 4. Results of regression analyses examining the association between physical activity with cognition

	Attention/executive function				Episodic memory				Language abilities			
	β	b	*SE* b	*p*	β	b	*SE* b	*p*	β	b	*SE* b	p
Block 1												
Constant	—	20.15	19.89	.32	—	37.53	6.82	<.01	—	48.33	5.76	<.01
Age	−0.26	−0.48	0.27	.09	−0.33	−0.22	0.09	.02	−0.30	−0.16	0.08	.045
Sex (1 = males; 0 = females)	−0.11	−3.69	5.09	.47	−0.29	−3.70	1.75	.04	0.13	1.34	1.47	.37
Ejection fraction	0.04	0.05	0.18	.79	−0.06	−0.03	0.06	.67	−0.10	−0.04	0.05	.50
Depression (1 = yes; 0 = no)	−0.26	−10.92	6.46	.10	0.06	−0.86	2.21	.70	0.05	0.57	1.87	.76
F		1.24 (p = .31)				2.80 (p = .04)				1.59 (p = .19)		
R^2		0.10				0.20				0.12		
Block 2												
Constant	—	6.16	20.05	.76	—	33.16	6.94	<.01	—	43.70	5.70	<.01
Average daily steps per day	0.31	0.003	0.00	.03	0.27	0.001	0.00	.049	0.35	0.001	0.00	.01
F Δ		5.03 (p = .03)				4.11 (p = .049)				6.85 (p = .01)		
Δ R^2		0.09				0.07				0.12		
Model F		2.09 (p = .085)				3.21 (p = .02)				2.81 (p = .03)		
Model R^2		0.19				0.27				0.24		

Note. Beta values for constants are unstandardized beta coefficients.
β = standardized beta coefficient; SE b = standard error of the unstandardized beta coefficient.

cognitive domains among older adults with HF. However, the mechanisms for this phenomenon had not yet been examined in HF and findings in other heterogeneous vascular disease populations have been limited by self-report assessments of PA. The current study extends the literature in HF by showing that daily PA was associated with larger subcortical brain volume, which in-turn, predicted cognitive function.

Table 5. Results of regression analyses examining the association between physical activity with subcortical brain volume

	Subcortical volume			
	β	b	*SE* b	*p*
Block 1				
Constant	—	123821.62	40983.32	<.01
Age	−0.15	−373.10	362.11	.31
Sex (1 = males; 0 = females)	0.09	4098.63	9451.26	.67
Ejection fraction	−0.02	−35.07	240.28	.89
Depression (1 = yes; 0 = no)	0.08	4581.98	8574.49	.60
Intracranial volume	0.36	0.05	0.03	.08
F		1.91 (p = .11)		
R^2		0.18		
Block 2				
Constant	—	122054.72	39380.82	<.01
Average daily steps per day	0.30	3.34	1.54	.04
F Δ		4.67 (p = .04)		
Δ R^2		0.08		
Model F		2.50 (p = .04)		
Model R^2		0.26		

Note. Beta values for constants are unstandardized beta coefficients.
β = standardized beta coefficient; SE b = standard error of the unstandardized beta coefficient.

Greater daily PA was associated with larger subcortical volume, which was then associated with better attention/executive function. To date, no other study has examined the impact of objectively measured PA on neuroimaging indices in patients with HF, and work in healthy older adults is limited. There is one study in older adults that demonstrated higher PA attenuated age-related prefrontal metabolic abnormalities during an fMRI reaction time task paradigm (Kimura et al., 2013). Other research examining accelerometer-assessed PA and brain outcomes has been in older adults with neurological impairment, and evidence in these populations suggests that PA is correlated with brain volume, including volume of subcortical brain regions (Doi et al., 2015; Makizako et al., 2015; Varma et al., 2015). The positive impact of PA on cognition in older adults, including executive functions, provides additional evidence for the association between PA and brain plasticity in normative aging populations (Barnes et al., 2008; Brown et al., 2012; Buchman, Wilson, & Bennett, 2008; Buchman et al., 2012; Wilbur et al., 2012). Yet, given the patterns of cognitive impairment observed in this study, a small subset of participants in this sample may have mild or vascular cognitive impairment, but even this cohort likely benefited from the neurological benefits of PA given promising findings in other neurological samples such as AD (Farina et al., 2014). Taken together, the current findings are largely consistent with the limited research that demonstrates the neurocognitive benefits of daily PA. However, much more work that uses objective assessments of PA and other rigorous methods (e.g., controls and comparison groups) is needed to better understand the impact of PA on the brain in older adults.

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We found that PA demonstrated regional effects for the thalamus and ventral diencephalon. Such findings are interesting, as HF patients exhibit atrophy of diencephalic structures relative to healthy controls (Woo et al., 2009) and these brain regions are implicated in cognitive functions, particularly memory abilities (Acosta-Cabronero & Nestor, 2014; Hunkin, Awad, & Mayes, 2015). In contrast to the extant evidence in neurological and older adult samples (Erickson et al., 2010; Makizako et al., 2015; Smith et al., 2014; Varma et al., 2015), PA was not associated with medial temporal lobe structures (e.g., hippocampus, entorhinal cortex) in this study. Methodological limitations (e.g., MRI protocol) may partially explain our null findings for medial temporal regions. For example, the slice thickness parameters used in this study is routine in clinical settings, though it may have been insufficient to capture small effects to tiny, deep, subcortical medial temporal lobe structures such as the hippocampus. The impact of PA on neurological outcomes may also be unique in the setting of cerebrovascular disease and involve heightened sensitivity to diencephalic regions. There is some support for this notion in research among stroke patients that has linked treadmill training with increased brain activity among the thalamus (Enzinger et al., 2009). There may also be a PA intensity threshold effect for regions that compose the medial temporal lobe that was not reached in this neurologically at-risk sample. In fact, in certain patient populations (including HF), greater amounts of PA may be needed to benefit brain structures that are vulnerable to pathological changes (e.g., hippocampus). As an example, moderately intense, but not light, PA has been linked with hippocampal volume in patients with MCI (Makizako et al., 2015). Yet, light PA has been shown to be sufficient to benefit the hippocampus in older adults without dementia (even after controlling for cardiovascular disease; Varma et al., 2015). The positive association between PA and neurological outcomes may also be capturing a subset of individuals who have cognitively benefited from participation in a lifelong pattern of healthy living. Future work should elucidate the nature of PA benefits on the brain across patient populations and whether there is a differential dose-response relationship across various brain regions.

There are several possible explanations for the positive effects of PA on the brain in HF. Patients with HF are sensitive to vascular benefits that accompany PA and can promote brain integrity, including increased cardiorespiratory fitness and better microvascular functioning (e.g., arterial plasticity, endothelial functioning; Alosco et al., 2013a; Athilingam et al., 2013; Klenk et al., 2013; Miralbell et al., 2012; Tsao et al., 2013; Zhang et al., 2013). The positive impact of PA on the function and structure of the brain likely translates to better cognitive abilities in HF, as is supported by previous work that directly links brain volume with mental functions in HF (Alosco et al., 2013b). Interestingly, the specific relationship between subcortical volume and attention/executive function in this study is consistent with the frontal subcortical clinical presentation typically observed in vascular disease populations (Sachdev et al., 2004). Longitudinal work in larger samples that assesses cerebrovascular function is needed to clarify the exact mechanisms by which PA promotes brain integrity and neurocognitive outcomes in HF.

Although case-controlled work in larger samples is needed to confirm our findings, it is possible that PA may attenuate cognitive decline and more severe neurological conditions (e.g., dementia) in HF *via* benefits on subcortical structures. There is some evidence that PA attenuates age-related cognitive decline and AD risk (Buchman et al., 2012; see Erickson et al., 2012, for a review) *via* increased brain plasticity (Erickson et al., 2012; Hayes, Hayes, Cadden, & Verfaellie, 2013; Okonkwo et al., 2014). A similar phenomenon may be evident in HF. For instance, recent longitudinal work suggests that daily PA and participation in exercise interventions may mitigate cognitive decline in HF (Alosco et al., 2014, 2015). These findings may in part be related to changes in the cerebral structure given work that links cardiovascular rehabilitation with increased gray matter volume among patients with coronary artery disease (Anazodo, Shoemaker, Suskin, & St Lawrence, 2013). Prospective studies with long-term follow-ups are needed to determine whether PA can reduce risk for accelerated age-related cognitive decline in HF through attenuation of brain degradation.

The current study is not without limitations. First, the lack of a control group precludes complete understanding of the relationships between PA, brain structure, and cognition in HF. Studies that implement healthy controls and comparison groups are needed to better control for demographic and medical confounds, and therefore clarify the nature and magnitude of the relationships among HF, PA, subcortical brain volume, and cognitive function. Longitudinal work is also needed to determine whether PA can attenuate brain atrophy and cognitive decline in HF, particularly as HF duration increases and cardiac severity worsens and risk for more severe forms of cognitive impairment (e.g., dementia) becomes higher. The relatively modest sample size of the sample also presents with statistical power concerns and may have limited detection of small effect sizes, and serve as another possible explanation for the lack of association between PA and medial temporal lobe regions. Larger sample sizes will not only increase external validity, but also reduce concerns for factors such as type 1 error *via* implementation of model-based approaches to simultaneously examine PA, brain structure, and cognition. Similarly, the current sample was relatively mild in disease severity (e.g., mean LVEF =43.22) and homogenous in terms of cognitive, demographic, and clinical make-up and more diverse samples will provide greater insight into PA and neurological status among older adults with HF. As an example, the mild and range restricted disease and cognitive status of the present sample may partially explain the unexpected lack of association between ejection fraction and neurocognitive outcomes in this study. However, a better understanding of the possible impact of mild HF on cognitive function is much

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needed, as other work shows that even subtle dysfunction can lead to poorer adherence (Alosco, Spitznagel, van Dulmen, et al., 2012) and increased mortality in this high risk population (Zuccala et al., 2003).

PA was associated with memory and language in this study, but these cognitive domains were not predicted by subcortical volume. It is possible that mechanisms not examined in this study may have contributed to the relationship between PA and cognition. As an example, PA has been shown to interact with genetic markers (e.g., APOE e4) to yield hippocampal volume benefits in cognitively intact older adults (Smith et al., 2014) and a similar phenomenon may be present in this population. Similarly, PA may have indirectly benefited memory and language *via* improved limbic-diencephalic white matter network connectivity (Tian et al., 2015, 2014) and studies that use diffusion tensor imaging and functional neuroimaging should explore this possibility.

In brief summary, greater PA was associated with increased subcortical volume, which in turn, was associated with better cognitive function. This study provides further evidence for PA as a protective factor against neurological impairment possibly *via* volumetric brain benefits. Longitudinal work with extended follow-ups (e.g., 2–5 years) is needed to test whether increased PA can attenuate brain changes and reduce risk for cognitive decline in HF.*

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