Published in final edited form as:

J Clin Exp Neuropsychol. 2013 March ; 35(3): 309–318. doi:10.1080/13803395.2013.771617.

The Adverse Impact of Type 2 Diabetes on Brain Volume in Heart Failure

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Abstract

Objective—Heart failure (HF) is associated with structural brain abnormalities, including atrophy in multiple brain regions. Type 2 diabetes mellitus (T2DM) is a prevalent comorbid condition in HF and is associated with abnormalities on neuroimaging in other medical and elderly samples. The current study examined whether comorbid T2DM exacerbates brain atrophy in older adults with HF.

Methods—Seventy-five older adults with HF underwent echocardiogram, and completed a brief cognitive test battery. Participants then underwent brain magnetic resonance imaging (MRI) to quantify total brain volumes, cortical lobar volumes, and white matter hyperintensities (WMH).

Results—Approximately 30% of HF patients had a comorbid T2DM diagnosis. A series of MANCOVA analyses adjusting for medical and demographic characteristics and intracranial volume showed that HF patients with T2DM had smaller total brain, gray matter, and subcortical gray matter volume than those without such history. No between group differences emerged for WMH. Persons with T2DM also had smaller cortical lobar volumes, including in frontal, temporal, and parietal lobes. Follow-up analyses revealed smaller total and cortical lobar brain volumes and WMH were associated with poorer performance on measures of global cognitive status, attention, executive functions, and memory.

Conclusions—T2DM is associated with smaller total and cortical lobar brain volumes in patients with HF and these structural brain indices were associated with cognitive test performance. Prospective studies that directly monitor glucose levels are needed to confirm our findings and clarify the mechanisms by which T2DM adversely impacts brain atrophy in this population.

Keywords

Brain; cognitive function; heart failure; type 2 diabetes; neuroimaging

1. Introduction

Heart failure (HF) has become an increasingly recognized risk factor for poor neurocognitive outcomes, including Alzheimer's disease and vascular dementia (Qiu et al., 2006; Roman, 2005). Before onset of these conditions, 30% to 80% of HF patients exhibit impairments in multiple cognitive domains, including attention, executive function, memory, and psychomotor speed (Vogels, Scheltens, Schroeder-Tanka, & Weinstein, 2007; Pressler et al., 2010). These cognitive deficits are believed to stem from the adverse effects of HF on the brain (Serber et al., 2008). Indeed, relative to controls HF patients exhibit greater atrophy in multiple brain regions and structural brain injury has been linked with reduced neuropsychological test performance in this population (Woo, Kumar, Macey, Fonarow, & Harper, 2009; Serber et al., 2008). Ischemic brain injury (i.e., white matter hyperintensities; WMH) has also been shown to be more prevalent in HF patients compared to healthy and cardiac controls (Vogels et al., 2007).

The mechanisms underlying these adverse brain changes are unclear and likely involve multiple physiological processes. Cardiac dysfunction and subsequent cerebral hypoperfusion are viewed as the most prominent contributors to brain insult in HF (Jefferson et al., 2007; Jesus et al., 2006; Gruhn et al., 2001). Cerebral blood flow is reduced in up to 30% of HF patients and is theorized to produce structural brain changes through deprivation in oxygen and nutrients and resulting ischemic injury, including white matter hyperintensities (WMH), axonal loss, rarefaction of myelin, gliosis, and fiber loss (Gruhn et al., 2001; Hoth, 2010; Pantoni & Garcia, 1997; Fazekas et al., 1993; Munoz, Hastak, Harper, Lee, & Hachinski, 1993). Indeed, cardiac dysfunction and cerebral hypoperfusion have both been linked to poorer cognitive test performance, greater WMH, and reduced total brain volume in HF and other CVD populations (Hoth, 2010; Loncar et al., 2011; Jefferson et al., 2010; Vogels et al., 2007a; 2007b).

Growing evidence links common medical and clinical comorbidities of HF (e.g., hypertension, sleep apnea) with poor neurocognitive outcomes. Type 2 diabetes mellitus (T2DM) is found in as many as 31% of HF patients and is associated with greater deficits in cognitive function relative to HF patients without T2DM (Braunstein et al., 2003; Alosco et al., 2012). Extant literature links T2DM to structural brain differences in persons with other medical conditions and older adults. For example, independent of HF, T2DM patients exhibit accelerated cognitive decline that is associated with corresponding total brain atrophy (Reijmer et al., 2011). Consistent with this notion, pronounced cortical and subcortical atrophy is also evident in T2DM patients and may in part explain the increased risk for dementia in this population (van Harten, de Leeuw, Weinstein, Scheltens, & Biessels, 2006; Arvanitakis, Wilson, Bienias, Evan, & Bennett, 2004; Raz & Rodrigue, 2006).

T2DM likely exacerbates adverse brain changes in HF through several pathophysiological mechanisms, including poor glycemic control and resulting cerebral micro- and macrovascular damage. For example, insulin resistance in the brain is common in T2DM and associated with cell apoptosis, reduced metabolism, decreased neuronal plasticity, and higher levels of amyloid beta (de la Monte, Longato, Tong, & Wands, 2009; Farris et al., 2003). There is also reason to believe that T2DM may lead to poor neurocognitive outcomes in HF patients through additive ischemic injury stemming from greater reductions in

cerebral blood flow. Supporting such mechanisms is past work showing that T2DM is associated with cerebral hypoperfusion, WMH, and increased oxidative stress (Su et al., 2008; Novak et al., 2006).

Despite these findings, the possible additive effects of T2DM on neurocognitive outcomes in older adults with HF are not well understood. The purpose of the current study was to examine whether HF patients with T2DM have smaller brain volumes in addition to poorer cognitive function than HF patients without T2DM. In light of the adverse effects of both HF and T2DM on cerebral hemodynamics, we also sought to examine whether HF patients with T2DM exhibit greater WMH volume than HF patients without T2DM.

2. Methods

2.1 Participants

The sample consisted of 75 persons with HF from a National Institutes of Health funded study examining neurocognitive outcomes in HF. Data collection for this study has been ongoing since January 2009. All participants were recruited from outpatient cardiology clinics at Summa Health System in Akron, Ohio. Strict inclusion/exclusion criteria were chosen for entry into the study. 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. NYHA is one of the most commonly used systems to classify symptoms of heart disease and is based on the following scale: 1) no limitation of physical activity; 2) slight limitation of physical activity, and ordinary physical activity may result in adverse symptomatology; 3) marked limitations of physical activity and less than ordinary physical activity results in adverse symptomatology; and 4) inability to perform physical activity without discomfort and symptoms may occur at rest (American Heart Association, 2012).

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 use, renal failure, and sleep apnea. Participants for the current study were also excluded for any contraindications to magnetic resonance imaging (MRI) (e.g., pacemaker). Participants averaged 68.08 (SD = 8.06) years of age, 41.3% of them were women, and 82.2% Caucasian. Medical record review revealed that the current sample exhibited an average left ventricular ejection fraction (LVEF) slightly below normal levels (i.e., 55%–70%), but higher than what is typical observed in HF patients (e.g., LVEF of the current sample = 43.25 (SD = 14.13)). 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°. Whole-brain T2 and FLAIR images were also acquired to quantify WMH. For the T2-weighted images, twenty-one 5-mm thick slices were acquired with a 230 × 100 mm field of view with TR = 2910 and TE = 134. For the FLAIR images, twenty-one 5-mm slices were acquired with TR = 8500, TE = 115, and FOV = 220 × 75.

Morphometric analysis of brain structure was completed with FreeSurfer Version 5.1 (<http://surfer.nmr.mgh.harvard.edu>). Detailed methodology for regional and total volume derivation has been described in detail previously (Fischl & Dale, 2000; Fischl et al., 2002; Fischl, Sereno, & Dale, 1999; Fischl et al., 2004). FreeSurfer was used to perform image preprocessing (e.g. intensity normalization, skull stripping), then to provide both cortical and subcortical volume measures using the surface stream and the subcortical segmentation stream respectively. FreeSurfer performs such parcellations by registering images to a probabilistic brain atlas, built from a manually labeled training set, and then using this probabilistic atlas to assign a neuroanatomical label to each voxel in an MRI volume. Total brain volume, total grey matter volume, and subcortical grey matter volume were derived with the subcortical processing stream (i.e., “aseg.stats”). The cortical volumes of the brain regions constituting the frontal, temporal, parietal, and occipital lobes, as described in Desikan et al. (2006), were derived from the surface stream (i.e., “aparc.stats”) and added hemispherically to create a summary composite for each lobe.

2.2.2. White Matter Hyperintensities—Total white matter hyperintensities (WMH) volume was derived by a three-step operator-driven protocol that has been described in detail previously (Brickman et al., 2011; Gurol et al., 2006). Briefly, in Step 1, a threshold was applied to each FLAIR image to label all voxels that fell within the intensity distribution of hyperintense signal. In Step 2, gross regions-of-interest (ROI) were drawn manually to include WMH but to exclude other regions (e.g., dermal fat) that have similar intensity values. In Step 3, a new image is generated that contains the intersection of voxels labeled in Step 1 and those labeled in Step 2. The resulting image contains thus contains labeled voxels that are common in Step 1 and Step 2. The number of resulting voxels is summed and multiplied by voxel dimensions to derive a total volume score. We have shown the validity and reliability of this approach previously (Brickman et al., 2011).

2.2.3 Cognitive Function—A series of neuropsychological measures was administered to assess cognitive function. The Mini Mental State Examination (MMSE) was used to assess global cognitive function. It is a brief measure that assesses aspects of attention, orientation, memory, language, and calculation (Folstein, Folstein, & McHugh, 1975). Other specific neuropsychological measures that demonstrate strong psychometric properties that were used to assess attention, executive function, psychomotor speed, and memory include: Trail Making Test A and B (Dikmen, Heaton, Grant, & Temkin, 1999; Reitan & Wolfson 1993), Digit Symbol Coding (Dikmen et al., 1999; Wechsler, 1997), Letter Number Sequencing (Wechsler, 1997), Grooved Pegboard dominant and non-dominant hand (Klove, 1963; Ruff & Parker, 1993), and the California Verbal Learning Test-II (CVLT-II) Total Recall, Short Delay Free Recall, and Long Delay Free Recall (Delis, Kramer, Kaplan, & Ober, 2000). Raw scores for all neuropsychological tests were used in demographically adjusted analyses. Time in seconds was used as the outcome variable for Trail Making Test A and B and Grooved Pegboard and higher scores were reflective of worse performance for these tests.

2.2.4 Depressive Symptoms—The BDI-II is a commonly used checklist that assesses depressive symptoms with strong psychometric properties in medical populations (Arnau, Meagher, Norris, & Bramson, 2001; Beck, Steer, & Brown, 1996).

2.2.5 Demographic and Medical Characteristics—Diagnostic history of T2DM, along with other participant demographic and medical characteristics, was ascertained through medical record review and self-report. Specifically, a medical record review was conducted for all participants to corroborate self-report and ascertain a physician diagnosed history of T2DM. Based on this medical record review, participants were coded as either having a positive or negative diagnostic history of T2DM. See Table 1.

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. All HF patients then completed baseline cognitive testing and underwent magnetic resonance imaging (MRI).

2.4 Statistical Analyses

To examine the additive effects of T2DM on structural brain volume, we used Multivariate Analysis of Covariance (MANCOVA). In the model, total brain volume, total gray matter volume, subcortical gray matter volume, and WMH were the dependent variables. Current diagnostic history of T2DM (1 = positive diagnostic history; 0 = negative diagnostic history) served as the two-level independent dichotomous grouping variable. Demographic and medical variables served as covariates, and included years of age, sex (1 = male; 2 = female), depressive symptomatology (BDI-II scores), LVEF, diagnostic history of hypertension, elevated total cholesterol, and sleep apnea (1 = positive diagnostic history; 0 = negative diagnostic history for all), and intracranial volume. This analytic approach was then used to identify possible effects of T2DM on cortical lobar volumes for frontal, temporal, parietal, and occipital lobe and also on cognitive test performance. Lastly, follow up partial correlation analysis adjusting for age, sex, depressive symptomatology, LVEF, diagnostic history of hypertension, elevated total cholesterol, and sleep apnea, and intracranial volume was conducted to determine whether structural brain indices and cortical lobar brain volumes were associated with cognitive test measures.

3. Results

Descriptive Statistics

T2DM was found in 30.3% of HF patients in this sample. Independent samples *t*-tests and chi-square analyses found no differences between HF patients with and without T2DM for age, education, sex, depressive symptomatology, LVEF, or history of sleep apnea or elevated total cholesterol. However, HF patients with T2DM were more likely to have a history of hypertension. See Table 1.

T2DM and Structural Brain Volume

After adjusting for medical and demographic characteristics and intracranial volume, MANCOVA revealed a significant main effect of T2DM diagnosis on structural brain indices ($\Lambda = .73$, $F(4, 62) = 5.88$, $p < .01$) and cortical lobar volumes ($\Lambda = .81$, $F(4, 62) = 3.65$, $p = .01$). Posttests showed HF patients with T2DM exhibited smaller total brain volume ($F(1,65) = 5.16$, $p = .03$), total gray matter volume ($F(1,65) = 12.75$, $p < .01$), and subcortical gray matter volume ($F(1,65) = 10.31$), $p < .01$) compared to non-diabetic HF patients. There was no between group differences for WMH volume ($p > .05$). HF patients with T2DM also showed smaller frontal ($F(1,65) = 7.36$, $p = .01$), temporal ($F(1,65) = 5.36$, $p = .02$), and parietal lobes ($F(1,65) = 10.08$, $p < .01$). No such pattern emerged for the occipital lobe ($p > .05$). See Table 2 for a full summary of MANCOVA analyses.

Cognitive Function, Neuroimaging, and T2DM

MANCOVAs with medical and demographic indices as covariates revealed significant group differences between HF patients with and without T2DM on measures of cognitive function ($\Lambda = .68$, $F(10, 57) = 2.65$, $p = .01$). HF patients with T2DM performance worse on the CVLT-II Short Delay Free Recall ($F(1,66) = 4.38$, $p = .04$), Long Delay Free Recall ($F(1,66) = 5.00$, $p = .03$), Digit Symbol Coding ($F(1,66) = 4.20$, $p = .04$), and on the

Grooved Pegboard dominant ($F(1,66) = 5.31, p = .02$) and non-dominant hand ($F(1,66) = 9.82, p < .01$) than HF patients without T2DM. There was a strong trend for Letter Number Sequencing ($F(1,66) = 3.33, p = .07$). No such pattern emerged for the CVLT-II Total Recall, Trail Making Test A or B or for the MMSE ($p > .05$ for both). See Table 3.

Finally, partial correlation analyses showed associations between total gray matter volume, WMH, and frontal, temporal, parietal, and occipital lobar volume with several neuropsychological tests assessing global cognitive status, attention, executive function, and memory. In each case, smaller brain volumes were associated with poorer test performance. See Table 4.

4. Discussion

Reduced brain volume is common in HF patients and believed to result from cardiac dysfunction and subsequent cerebral hypoperfusion. The current study extends these findings by showing that T2DM—a prevalent comorbid medical condition—may also independently contribute to changes in total and cortical lobar brain volumes in HF. Our findings also demonstrate the association of reduced brain volumes with poorer cognitive performance in HF. Several aspects of these findings warrant brief discussion.

We observed smaller total brain, total gray matter, and subcortical gray matter volume in HF patients with T2DM than in those without that condition. These findings are consistent with past studies linking T2DM to accelerated cerebral atrophy in elderly patients (De Bresser, Tiehuis, & van de Berg, 2011; Reijmer et al., 2011). There are several possible pathophysiological explanations for these effects. First, insulin resistance in the brain is common among patients with T2DM and is linked with cell apoptosis, reduced metabolism, and decreased neuronal plasticity—all factors that can adversely impact the integrity of brain structure (de la Monte et al., 2009). In addition, endothelial dysfunction stemming from poor glycemic control is a common vascular consequence of T2DM and may exacerbate the existing cerebral hypoperfusion in HF patients (Toda, 2012). Cerebral hypoperfusion is an established risk factor for cognitive impairment in HF and extant evidence demonstrates its negative influences on brain structure in HF patients and in T2DM patients (e.g., reduced brain volume; Jefferson et al., 2007; Jesus et al., 2006; Gruhn et al., 2001; Brundel, Deary, & Ryan, 2012). It is also possible that other physiological effects of T2DM, such as atherosclerosis, chronic hyperglycaemia, and microvascular complications (Biessels et al., 2008), may contribute to structural brain changes in this population. Longitudinal studies are needed to clarify the mechanisms by which T2DM adversely impacts brain volume in older adults with HF, particularly as it relates to cerebral hemodynamics.

The current study found adverse effects of T2DM in multiple cortical lobar regions, including smaller volumes for frontal, temporal, and parietal lobes. This finding is consistent with past work demonstrating gray matter atrophy of these regions in HF. The affected regions include structures involved in cognitive, autonomic, and respiratory functions (e.g., insula, parahippocampus, frontal cortex, medial temporal lobe; Woo, Macey, Fonarow, Hamilton, & Harper, 2003; Serber et al., 2008). These findings suggest that T2DM exacerbates structural damage to these brain regions in HF and may help to explain the increased risk for Alzheimer's disease in older adults with HF (Qiu et al., 2006). For instance, hyperinsulinemia is correlated with greater levels of amyloid beta—an early indicator of Alzheimer's pathogenesis that is also associated with atrophy of the hippocampus and medial frontal and parietal brain regions (Yates et al., 2011; Chetelat et al., 2012; Chetelat et al., 2010). Lastly, our study did not find a significant association between T2DM and WMH in this sample of HF patients. The literature is mixed regarding

the association between T2DM and WMH volumes (van Harten, Oosterman, Potter van Loon, Scheltens, & Weinstein, 2007; Korf, White, Scheltens, & Launer, 2006) and such inconsistencies may be a result of differing methodology in the quantification in WMH. For instance, past studies that do not use fluid-attenuated inversion recovery (FLAIR) sequencing may have missed WMH (Rydborg et al., 1994; Alexander, Shappard, Davis, & Salverda, 1996; Herskovits, Itoh, & Melhem, 2001). Similarly, previous studies use of semi-quantitative methodology for estimating WMH may also in part explain evidence showing a lack of association between T2DM and WMH (den Heijer et al., 2003; Schmidt et al., 2004). Prospective studies in HF will clarify the modifying effects of T2DM on structural brain changes in this population and whether such changes lead to greater risk for Alzheimer's disease.

Finally, HF patients with T2DM performed worse on several measures of cognitive function and these deficits were associated with reduced total and cortical lobar brain volumes. Such findings suggest that T2DM may exacerbate cognitive impairment in HF through its adverse effects on brain volume. Continued work in this area will help clarify the mechanisms by which T2DM produces both structural and functional brain changes and their relative contribution to cognitive impairment over time.

The current findings are limited in several ways. First, T2DM history was operationalized through medical chart review. This approach has previously been used to document the adverse effects of T2DM on neurocognitive outcomes, including increased risk for Alzheimer's disease (Arvanitakis, Wilson, Bienias, Evans, & Bennett, 2004). However, prospective studies that use sophisticated glucose monitoring or clinical laboratory tests (e.g., oral glucose tolerance test) will be instrumental in the validation of the additive effects of T2DM on the brain in HF patients. Consistent with this notion, past work shows history of T2DM is associated with poorer cognitive function in the elderly (Grodstein, Chen, Wilson, & Manson, 2001) and future work should examine whether T2DM duration is a more sensitive measure of brain damage relative to current disease severity. Such work should also examine the impact of diabetic medication on neurocognitive outcomes in HF. Similarly, future studies should use echocardiogram and other objective measures to assess the impact of current comorbid medical status (e.g., hypertension, sleep apnea) on brain volume and cognitive function in HF.

In addition, our findings are based on cross-sectional data among a relatively small sample size of HF patients. Thus, larger longitudinal studies are needed to ascertain whether T2DM accelerates cerebral atrophy in HF. Longitudinal studies in T2DM suggest that atrophy is likely (de Bressler et al., 2011) and may have important implications for understanding the association between HF and outcomes like vascular dementia and Alzheimer's disease (Qiu et al., 2006; Roman, 2005). Future studies are also needed to determine the exact etiological mechanisms that produce structural brain changes in HF patients with T2DM by using advanced neuroimaging techniques such as positron emission tomography (PET) or arterial spin labeling (ASL). Such studies would help clarify whether cerebral hypoperfusion, physiological processes specific to diabetes (e.g. hyperinsulimnia), or their combination accounts for the reduced brain volumes found in the current study.

In brief summary, HF patients with T2DM exhibited smaller total and cortical lobar brain volume and these structural brain indices were also associated with cognitive test performance in this sample of HF patients. Prospective studies are needed to elucidate underlying mechanisms for the association between T2DM and reduced brain volumes in HF and whether these changes predict long-term outcomes like stroke or Alzheimer's disease.

Acknowledgments

Support for this work included National Institutes of Health (NIH) grants DK075119 and HLO89311. Dr. Naftali Raz is also supported by National Institutes of Health (NIH) grant R37 AG011230. The authors have no competing interests to report.

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Table 1

Demographic and Medical Characteristics of Older Heart Failure Adults with and without Type-2 Diabetes Mellitus (DM)

Demographic Characteristics	Heart Failure w/o T2DM	Heart Failure w/ T2DM	Total Sample	χ^2/t statistic
<i>N</i>	52	23	75	75
Age, mean (SD)	68.96 (8.51)	66.09 (6.67)	68.08 (8.06)	-1.43
Sex (% Women)	38.5	47.8	41.3	.58
Years of Education, mean (SD)	14.04 (2.87)	13.48 (2.15)	13.87 (2.67)	-.84
Medical Characteristics				
LVEF, mean (SD)	42.33 (13.18)	43.35 (16.21)	43.25 (14.13)	.85
BDI-II, mean (SD)	6.35 (6.80)	6.04 (5.04)	6.25 (6.28)	-.19
Hypertension (%)	65.4	91.3	73.3	5.48 *
Sleep Apnea (%)	23.1	39.1	28.0	2.04
Elevated Total Cholesterol (%)	59.6	78.3	65.3	2.45

Note. LVEF = Left Ventricular Ejection Fraction;

* $p < .05$

Table 2

Means and Standard Deviations (Means(SD)) of Structural Brain Volume Indices for Heart Failure Patients With and Without Type-2 Diabetes Mellitus

	Total Brain	Total Gray	Subcortical Gray	WMH
HF w/ T2DM (<i>N</i> = 23)	974204.44(142141.38)	515685.97(67640.73)	158438.65(23763.17)	13.03(11.89)
HF w/o T2DM (<i>N</i> = 52)	1015255.50(135785.86)	557188.27(64075.31)	171219.04(21746.90)	13.04(11.28)
<i>F</i>	5.16 [*]	12.74 ^{**}	10.31 ^{**}	.36
<i>Partial eta squared</i>	.07	.16	.14	.01
	Frontal	Temporal	Parietal	Occipital
HF w/ T2DM (<i>N</i> = 23)	148365.70(23379.45)	79892.61(15543.99)	98121.30(14226.76)	37171.00(6562.35)
HF w/o T2DM (<i>N</i> = 52)	160407.71(1984.27)	86582.46(14198.89)	107836.10(14835.99)	38180.63(6172.21)
<i>F</i>	7.36 [*]	5.36 [*]	10.08 ^{**}	.09
<i>Partial eta squared</i>	.10	.08	.13	.00

Note.

^{*}
p < .05;

^{**}
p < .01

Abbreviations—HF w/ T2DM = Heart Failure with Type-2 Diabetes Mellitus; HF w/o T2DM = Heart Failure without Type-2 Diabetes Mellitus; WMH = White Matter Hyperintensities

Table 3

Means and Standard Deviations (Means(SD)) of Cognitive Test Measures for Heart Failure Patients With and Without Type-2 Diabetes Mellitus

	HF w/T2DM (N =23)	HFw/oT2DM (N = 52)	F	Partial Eta
MMSE	27.70(1.66)	27.63(2.06)	.01	.00
TMTA	42.09(14.72)	38.67(13.38)	1.06	.02
TMTB	127.78(81.94)	111.35(60.44)	1.31	.02
Digit Symbol	47.26(13.16)	53.65(12.92)	4.20 *	.06
LNS	8.91(2.28)	9.75(2.40)	3.33 Ψ	.05
PegD	111.48(34.26)	96.81(22.71)	5.31 *	.07
PegND	127.91(32.05)	107.23(27.08)	9.82 **	.13
CVLTTotal	41.78(11.32)	40.98(11.69)	.44	.01
CVLTSDFR	7.04(2.65)	7.94(3.36)	4.38 *	.06
CVLTLDFR	7.70(2.62)	8.42(3.89)	5.00 *	.07

Note.

* $p < .05$;

** $p < .01$;

Ψ $p = .07$

Abbreviations—HF w/ T2DM = Heart Failure with Type-2 Diabetes Mellitus; HF w/o T2DM = Heat Failure without Type-2 Diabetes Mellitus; TMTA = Trail Making Test A; TMTB = Trail Making Test B; Digit = Digit Symbol Coding; LNS = Letter Number Sequencing; PegD = Grooved Pegboard Dominant Hand; PegND = Grooved Pegboard Non-dominant Hand; CVLT = California Verbal Learning Test; SDFR = Short Delay Free Recall; LDFR = Long Delay Free Recall

Table 4

Partial Correlations Examining the Association between Neuroimaging and Cognitive Test Performance

<i>Cognitive Test Measure</i>	<i>Volumetric Indices</i>						
	Gray	SubCort Gray	Frontal	Temporal	Parietal	Occipital	WMH
MMSE	.30*	.08	.29*	.26*	.25*	.29*	-.22 ^ψ
CVLT Total	.26*	.20	.16	.16	.18	.25*	.00
CVLT SDFR	.27*	.13	.26*	.20	.20	.13	-.13
CVLT LDFR	.36**	.21	.33*	.25*	.28*	.26*	.01
TMTA	-.35**	-.17	-.35**	-.19	-.42**	-.26*	-.01
TMTB	-.36*	-.23	-.33**	-.24*	-.37**	-.22	.03
Digits	.43**	.13	.42**	.37**	.44**	.23	-.05
LNS	.17	.17	.17	.06	.16	.01	-.15
PegD	-.55**	-.18	-.58**	-.44**	-.54**	-.30**	-.14
Peg ND	-.58**	-.21	-.57**	-.46**	-.57**	-.39**	-.03

Note.

* $p < .05$;

** $p < .01$;

^ψ $p = .07$

MMSE = Mini Mental State Examination; CVLT = California Verbal Learning Test; SDFR = Short Delayed Free Recall; LDFR = Long Delayed Free Recall; TMTA = Trail Making Test A; TMTB = Trail Making Test B; Digits = Digit Symbol Coding; LNS = Letter Number Sequencing; PegD = Grooved Pegboard dominant hand; Peg ND = Grooved Pegboard non-dominant hand; Gray = Total Gray Matter Volume; SubCort Gray = Subcortical Gray Matter Volume; WMH = White Matter Hyperintensities
Correlations were adjusted for age, sex, depressive symptomatology (as assessed by the BDI-II), LVEF, diagnostic history of hypertension, elevated total cholesterol, and sleep apnea, and intracranial volume.