Neuropsychology Review
https://doi.org/10.1007/s11065-020-09463-3

REVIEW

Neuropsychological Assessment and Screening in Heart Failure: a Meta-Analysis and Systematic Review

Eric J. Connors[1,2,3] · Alexander O. Hauson[1,3,4] · Brianna D. Barlet[1,3] · Sharis Sarkissians[1,3] · Nicholas P. Stelmach[1,3] · Alyssa D. Walker[1,3] · Natasha M. Nemanim[1,3] · Kristina L. Greenwood[5] · Nicholas J. Chesher[5] · Scott C. Wollman[1,3] · Kenneth E. Allen[1,3] · Matthew G. Hall[1,3] · Christopher Flora-Tostado[1,3]

Received: 9 January 2020 / Accepted: 12 October 2020

Abstract

A variety of neuropsychological changes secondary to heart failure have been documented in the literature. However, what remains unclear are which neuropsychological abilities are the most impacted by heart failure and what tests have the sensitivity to measure that impact. Eight databases were searched for articles that examined the neuropsychological functioning of patients with heart failure. Some of the inclusion criteria were articles had to have a heart failure group with a demographically comparable control group and standardized neuropsychological testing. Exclusion criteria included articles with a heart failure group with any other type of major organ failure, or comparisons that were between different classes of heart failure rather than between a heart failure and non-heart failure group. A total of 33 articles met the inclusion criteria (total heart failure sample n = 8900) and provided effect size data for 20 neuropsychological domains. All observed domain-level differences between heart failure and non-heart failure groups were statistically significant, except for simple motor functioning and confrontation naming. The greatest differences in performance were in executive functioning, global cognition, complex psychomotor speed, and verbal memory. The highest effect sizes came from Trail-Making Test-Part B, CAMCOG, Symbol Digit Modality Test, and California Verbal Learning Test. The neuropsychological patterns of heart failure suggested diffuse cognitive involvement, with higher-level processes being most affected. It is important to track neurocognition in this clinical population since neuropsychological impairment is prevalent, and screening measures appear to be reliable. Such screening and further assessment would inform future medical treatment and may improve patient care management.

Keywords Heart failure · Neuropsychology · Meta-analysis · Executive function · Memory · Global cognition

The heart-brain connection has been well-documented in the literature, and there are neurophysiological as well as neuropsychological sequelae when the heart fails. Heart failure occurs when the heart is incapable of providing the body with adequate blood flow resulting in decreased oxygenation (Mozaffarian et al., 2016). Once the brain recognizes lowered cardiac output, it compensates by activating the sympathetic nervous system (SNS) to increase heart rate, heart contractions, and vasoconstriction (Kemp & Conte, 2012). This compensatory process, known as the Frank-Starling Mechanism, contributes to the degenerative nature of heart failure as chronic stimulation of the SNS further weakens the heart muscle (i.e., myocardium) and increases vascular resistance (Kemp & Conte, 2011). Subsequently, weakened myocardium and rigid vasculature leads to chronic poor blood oxygenation and low cardiac output which have additional adverse effects on the brain (Athilingam, D'Aoust, Miller, & Chen, 2013; Frey et al.,

✉ Alexander O. Hauson
alexanderhauson@gmail.com

1 California School of Professional Psychology, Clinical Psychology PhD Program, San Diego, CA, USA

2 Department of Psychiatry, Massachusetts General Hospital, Harvard Medical School and Home Base, a Red Sox Foundation and Massachusetts General Hospital Program, Charlestown, MA, USA

3 Institute of Brain Research and Integrated Neuropsychological Services (iBRAINs.org), San Diego, CA, USA

4 Department of Psychiatry, University of California San Diego, La Jolla, CA, USA

5 Sharp HealthCare, San Diego, CA, USA

Published online: 11 January 2021

2018). Consistent with the course of vascular cognitive impairment (VCI), subcortical changes in white matter are thought to occur initially and as the disease process progresses, diffuse cortical changes follow (Caruso, Signori, & Moretti, 2019). These microstructural and macrostructural changes have been associated with functional impairment (Frey et al., 2018).

Cardiovascular disease, broadly, is considered to be an independent predictor of cognitive decline in older adults and this is particularly true in those with heart failure (Hammond et al., 2018). For instance, a recent epidemiological study, the Cardiovascular Health Study, found that heart failure was predictive of greater reductions in performance on global cognition and processing speed measures over the course of five years (Hammond et al., 2018). Similar findings have been supported in neuropsychological primary studies (Almeida et al., 2012; Beer et al., 2009; Kindermann et al., 2012; Pressler et al., 2010; Suavé, Lewis, Blankenbiller, Rickabaugh, & Pressler, 2009). For example, Suavé et al. (2009) investigated the neuropsychological performance of those diagnosed with heart failure using a battery of tests. When compared to well-matched controls, individuals diagnosed with heart failure performed about one standard deviation below the control group on measures of attention, immediate recall, and delayed recall. There was also a significant difference on complex psychomotor speed, whereas recognition memory and simple psychomotor scores did not yield significant between-group differences. Using odds ratios, the researchers concluded that individuals with heart failure had a four-fold risk for cognitive impairment when compared to matched controls (Suavé et al., 2009).

Similar results were found by Pressler and associates (2010), who found that individuals diagnosed with heart failure performed significantly worse on measures of complex psychomotor speed and verbal memory. Those in the heart failure group also performed significantly worse on measures of visuospatial ability and executive function. Additional analyses found that heart failure severity was associated with memory, visuospatial ability, psychomotor speed, and executive function performance (Pressler et al., 2010).

Cognitive impairment has also been found among individuals with heart failure who were awaiting surgical implantation of a left ventricular assist device (LVAD). For instance, Mapelli et al. (2014) found that such patients had impairments in executive function, visuospatial perception/drawing, memory, and attention. However, none of the participants scored in the impaired range on the Mini-Mental State Examination (MMSE). These researchers also found that story memory-immediate recall (Wechsler Memory Scale –WMS) and an interference memory test were the only two domains that improved following left ventricular assist device implantation (Mapelli et al., 2014). These findings, however, are inconsistent with those reported by Bhat, Yost, and Mahoney (2015), who conducted a study that screened patients' cognitive abilities pre- and post-left ventricular assist device implantation using the Montreal Cognitive Assessment (MoCA), a cognitive screening measure similar to the MMSE. The results from this study found that 67% of left ventricular assist device patients scored in the impaired range on the MoCA and that for a subset of individuals (35.7%), their performance significantly improved after implantation (Bhat et al., 2015). Moreover, those who scored in the impaired range performed significantly worse in every MoCA subdomain compared to those who scored in the normal range, suggesting diffuse cognitive decline associated with heart failure (Bhat et al., 2015). These findings also support the potential limitations of the MMSE in identifying cognitive impairments in this population.

More recently, Yohannes, Chen, Moga, Leroir, and Connolly (2017) conducted a meta-analysis that examined 17 studies focused on the prevalence of mild cognitive impairment (MCI) among those diagnosed with heart failure or chronic obstructive pulmonary disease (COPD) using screening measures. The majority of studies in this meta-analysis utilized the MMSE, MoCA, and Abbreviated Mental Test as cognitive screening measures. The results indicated that the rates of MCI were 32% in heart failure patients and 25% in those with COPD (Yohannes et al., 2017). Taken together, it was concluded that MCI is prevalent in those with heart failure and it is essential to broadly assess neuropsychological function in this clinical population (de la Torre, 2012; Weintraub, Wicklund, & Salmon, 2012).

The purpose of this meta-analysis was to determine the impact of heart failure on neuropsychological functioning. First, we investigated whether the neurocognitive effects of heart failure were diffuse or domain-specific. Second, we examined which domains are most impacted by the disorder. Finally, we highlighted the most commonly used assessment tools utilized in the evaluation of this population.

Method

The design and implementation of this meta-analysis was consistent with the guidelines of the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA; Gates & March, 2016; Moher et al., 2015). To minimize potential selection bias and ensure the accuracy of the data collected, two researchers independently completed every phase of this meta-analysis (i.e., identification, screening, eligibility, and data extraction). When there were discrepancies between any two researchers, a senior researcher with extensive experience in neuropsychological meta-analyses facilitated the discussion and then made the final decision based on consensus among raters and coders.

Search Strategy and Data Acquisition

An electronic search was conducted using databases that were relevant to the topic. These databases were (a) PsycINFO, (b) PUBMED, (c) Web of Science, (d) ProQuest Dissertations and Theses, (e) ArticlesFirst, (f) ProceedingsFirst, (g) PapersFirst, and (h) Academic Search Complete E-Journals. The researchers (E.C. & A.H.) tailored the search to each database and used broad terms to maximize the inclusion of relevant articles. There were no restrictions on country of origin, publication date, or publication status. These searchers included all relevant literature available up until April 2019.

Before initiating the search, the research team consulted cardiologists, cardiac nurse practitioners, and search specialists at PsycINFO and PUBMED to determine the best controlled and uncontrolled vocabulary for the search. The following terms and phrases were used: 'cardiomyopathy,' 'congestive heart failure,' 'diastolic dysfunction,' 'diastolic failure,' 'ejection fraction,' 'end-stage cardiovascular disease,' 'end-stage heart disease,' 'heart failure,' 'heart transplant,' 'systolic failure or dysfunction,' 'ventricular failure or dysfunction,' and 'ventricular or mechanical assist device.' The online searches integrated the heart failure terminology in combination with neuropsychological domains and well-known neuropsychological tests. The comprehensive list of terms that captured the neuropsychological domains and tests can be found in the published meta-analysis by Stephan et al. (2017) and in the supplemental material of this study.

In addition to the online search, the research team explored the reference list of all relevant primary studies and reviews to identify any other pertinent literature. This manual search involved 56 literature reviews related to heart failure and neurocognitive functioning. Together, the electronic and manual searches yielded 10,706 results, and following the removal of duplicates, two researchers independently sorted 9741 unique articles. Based on the article title and abstract, the articles were sorted and labeled 1) *relevant*, 2) *requires full-text review*, 3) *literature review,* or 4) *irrelevant. Irrelevant* studies included case examples, animal studies, and primary studies that recruited a pediatric sample or a sample without heart failure. Out of the 9741 articles collected, 254 articles underwent full-text review by two trained research assistants to determine if the study met the inclusion/exclusion criteria.

Inclusion and Exclusion Criteria

Primary studies in this meta-analysis were required to incorporate (a) adults with a diagnosis of heart failure, (b) an active control group with comparable demographics (e.g., groups matched on age), (c) standardized neuropsychological/cognitive testing, and (d) data that allows for the calculation of effect size (e.g., means, standard deviations, *t*- and *p*--values). Studies were excluded if (a) the heart failure group had other types of major organ failure (i.e., lung or liver failure), (b) the comparison was between different classes of heart failure (i.e., New York Heart Association (NYHA) Class II versus NYHA Class III), (c) the neuropsychological tests were administered in an unstandardized format or did not have published normative data (e.g., experimental neuropsychological tests), (d) the article was not published or translated into English, or (e) there was a risk of sample overlap with another included study.

Several factors were assessed to determine the possibility of overlapping samples that would violate the assumption of independence of observation across studies. As described in the Cochrane Review Handbook (Higgins & Green, 2011), it is essential to consider the first author, sample characteristics, outcomes (i.e., neuropsychological tests utilized), as well as the recruitment location and timeframe. When the likelihood of sample overlap was high, the research team included the study with the greater sample size (Borenstein et al., 2011). In some cases, studies with the same first author met inclusion criteria when the article stated that there was no sample overlap from previously published articles or if there was a distinct difference in the recruitment characteristics.

Data Extraction

After the full-text review, 33 articles met the inclusion and exclusion criteria (Fig. 1). Data were extracted using coding forms adopted from previous neuropsychological meta-analyses (Hall et al., 2018; Wollman et al., 2019). The study-related variables were (a) article title, (b) first author, (c) publication year, (d) article type (e.g., peer-reviewed or dissertation), (e) country, (f) recruitment setting, (g) the number of variables matched between groups, (h) sample size, and (i) age. Test variables consisted of (a) test name, (b) outcome measured, (c) group means and standard deviations or any other data that allows for effect size calculation, (d) sample size of groups that completed the test, and (e) type of score presented (i.e., raw score or standard score).

Quality of Study Assessment

A quality of study instrument was adapted based on the components of the psychometrically validated "Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies" created by the National Heart, Lung, and Blood Institute (2014). Before utilizing the assessment tool, five independent researchers (A.W., B.B., E.C., N.N., & N.S.) tested the instrument by assessing studies that were suspected of having low, medium, or high quality by the primary investigator. The tool underwent modification until the interrater reliability between the five researchers reached 90% across all study qualities.

The final quality of study assessment tool for this meta-analysis had 11 components that were designed to capture the

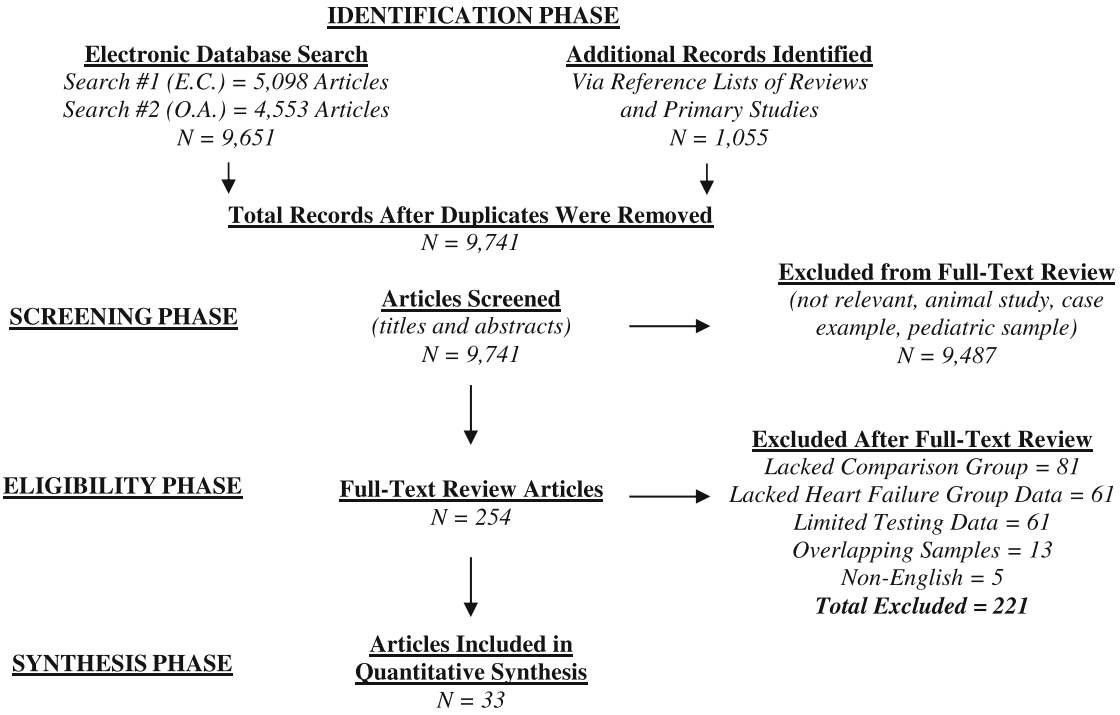

Fig. 1 PRISMA flowchart of articles identified, screened, reviewed and included in the final analyses

clarity of information reported, as well as the reliability and validity of the primary study. All items on the scale were scored using zero, one, or two points (i.e., 0, 1, 2), with 0 indicating a missing component or consideration, 1 indicating unclear reporting of an item, and 2 indicating transparent reporting of a component. The range of possible total scores was a minimum of zero and a maximum of 22, with higher scores indicating higher quality. The articles were divided into two groups, low quality versus high quality, based on a median-split of the total score.

The quality of study also assessed the internal and external validity of each study. Internal validity was determined by (a) evaluating if those administering the neuropsychological tests were blind to the group status of the participant, (b) ensuring similar time frame and location of testing across groups, and (c) considering if the two groups were comparable in age, education, and premorbid intellectual functioning. External validity was assessed by evaluating if the heart failure sample was representative of the typical heart failure population (e.g., included those with a range of heart failure severity) and treatment setting. The quality of study tool can be found in the supplemental material of this study.

Data Analysis

Two independent researchers (i.e., coders) extracted the variables of interest and completed the quality of study assessment for all 33 included studies (Table 1). In order to ensure accuracy in the data collected, a third-party researcher reviewed the data for discrepancies between the two coders and subsequently made the final decision. All of the data was imported into Comprehensive Meta-Analysis Version 2 (CMA). Consistent with recent neuropsychological meta-analyses (Hall et al., 2018; Goodall et al., 2018; Prado, Watt, & Crowe, 2018; Wollman et al., 2019), the pooling of effect sizes was done in CMA using the random-effects model.

Primary Analyses The testing data was organized by domain and each domain was analyzed as an independent meta-analysis. Domains were created when there were at least two shared test scores allowing for effect-size calculations. The organization of these test scores were based on previously published articles (Hall et al., 2018; Wollman et al., 2018), data provided by test manuals and compendiums (Strauss, Sherman, & Spreen, 2006), and evidence-based clinical interpretation found in major references about neuropsychological assessment (Lezak, Howieson, Bigler, & Tranel, 2012). In order to maintain the independence of observation at the domain-level, composite scores were created for studies that reported more than one test score in a single domain. When there were multiple heart failure groups (e.g., groups separated by severity) compared to one control group, the means and standard deviations of the two groups were pooled to create one composite score.

The pooled effect size for each test score and domain was measured and reported using Hedges' *g*. Hedges' *g* is considered robust when combining studies with different sample sizes or outcome variables, and these effect sizes are interpreted as small ($g < 0.49$), medium ($g = 0.50–0.79$), or

Table 1 Study characteristics of the 33 articles that met the inclusion criteria

Primary Study		Location	Sample Size *(n)*			Mean Age (SD)		*Domains Extracted*
First Author	Year		Total	HF	Control	HF	Control	
Adebayo et al.	2016	Nigeria	111	60	51	64.6 (14.6)	60.9 (14.6)	*Not applicable (excluded during analyses)*
Agarwal et al.	2016	USA	241	121	120	78.9 (4.8)	78.2 (5.6)	*GC*
Alagiakrishnan et al.	2017	Canada	53	33	20	72.8 (8.5)	75.1 (6.0)	*GC*
Almeida and Tamai	2001	Brazil	80	50	30	67.3 (6.1)	76.7 (7.7)	*A; CP; EF; GC; PS; VRM; WM*
Almeida et al.	2012	Australia	158	77	81	68.4 (10.2)	69.3 (11.3)	*CP; GC; VRM*
Alves et al.	2007	Brazil	41	23	18	73.2 (5.1)	72.8 (4.8)	*A; EF; GC; O; VRM*
Alwerdt et al.	2013	USA	2671	138	2533	74.9 (6.3)	73.5 (5.9)	*CFA; EF; G; VRM*
Beer et al.	2009	Australia	55	31	24	54.3 (10.6)	56.1 (8.2)	*GC; FI; VC; VRM; VSM*
Chou et al.	2014	USA	140	76	64	69.7 (10.2)	68.9 (7.1)	*GC; VRM; VSM; WM*
Grimm	1996	Austria	110	55	55	54.8 (9.2)	54.2 (NR)	*GC; PS*
Grubb et al.	2000	UK	40	20	20	66.7 (5.5)	66.4 (6.0)	*A; O; VRM; VSM; WM*
Habota et al.	2015	Australia	60	30	30	70.0 (11.9)	69.9 (6.0)	*EF; GC; FI; VRM; WM*
Hjelm et al.	2012	Sweden	702	95	607	84.3 (4.1)	83.3 (2.9)	*A; CFA; VC; VRM; VSM; WM*
Hoth et al.	2008	USA	62	31	31	69.1 (8.5)	68.9 (8.5)	*A; CFA; EF; FI; GC; PS; VC; WM*
Jung et al.	2016	USA	40	20	20	59.5 (12.8)	58.8 (11.6)	*A; CFA; EF; GC; PS; WM*
Kim et al.	2018	South Korea	201	118	83	65.5 (9.4)	66.0 (8.3)	*A; FI; VRM; WM*
Kure et al.	2016	Australia	76	36	40	68.0 (7.0)	67.0 (5.0)	*A; CFA; EF; GC; PS; VRM; WM*
Lavery et al.	2007	USA	354	68	286	78.8 (7.2)	77.2 (6.5)	*EF; FI; GC; PS; VC; VRM; VSM*
Meguro et al.	2017	Japan	37	20	17	74.2 (12.0)	73.8 (8.9)	*GC*
Moon et al.	2016	USA	841	97	744	84.8 (7.6)	81.3 (6.9)	*A; CP; FI; VRM; WM*
Moryś et al.	2016	Poland	100	50	50	56.0 (8.0)	56.0 (9.0)	*A; EF; FI; PS; VRM; WM*
Nikendei et al.	2016	Germany	47	24	23	70.4 (11.6)	69.8 (11.8)	*CFA; EF; PS; VSM; WM*
Nordlund et al.	2015	Sweden	81	40	41	73.0 (7.0)	67.0 (7.0)	*CP; EF; GC; N; VC; VRM*
Pressler et al.	2010	USA	312	249	63	62.9 (14.6)	53.3 (17.2)	*A; CP; EF; FI; GC; N; PS; VC; VRM; VSM; WM*
Putzke et al.	2000	USA	113	75	38	50.4 (11.1)	47.0 (9.1)	*EF; PS; SM; VRM*
Qiu et al.	2006	Sweden	1301	205	1096	83.3 (5.4)	81.2 (4.8)	*GC*
Roy et al.	2017	USA	48	19	29	55.5 (9.1)	51.4 (5.3)	*A; EF; GC; N; O; VC; VRM*
Sauvé et al.	2009	USA	100	50	50	63.0 (14.0)	62.5 (14)	*CFA; CPS; SM; VRM*
Schmidt et al.	1991	Austria	40	20	20	40.5 (7.8)	37.9 (4.7)	*CFA; VRM; VSM*
Stanek et al.	2009	USA	75	40	35	69.1 (8.7)	71.3 (6.1)	*A; EF; GC; VC; VRM*
Staniforth et al.	2001	UK	102	81	21	63.8 (1.0)	66.0 (1.4)	*CFA; EF; WM*
Trojano et al.	2003	Italy	515	308	207	74.7 (7.1)	73.7 (6.6)	*A; FI; GC; VRM; WM*
Vogels et al.	2007	Netherlands	104	62	42	69.2 (9.2)	67.2 (9.2)	*CFA; EF; Fl; GC; PS; VC; VRM; VSM*

Note. *A* attention, *CFA* concentration/focused attention, *CP* complex psychomotor, *EF* executive function, *FI* fluency/initiation, *GC* global cognition, *HF* heart failure, *N* naming, *n* sample size, *O* Orientation, *PS* processing speed, *SD* standard deviation, *SM* simple motor, *VC* visuospatial construction, *VRM* verbal memory, *VSM* visual memory, *WM* working memory

large *($g > 0.8$*; Cohen, 1992*)*. Along with the calculation of the effect size, the within- and between-group heterogeneity was assessed by the *Q*-statistic, I^2, and Tau^2. It is considered best-practice to report all three measures of heterogeneity as the Q-statistic is a metric of statistical significance, Tau^2 is representative of the true expected variance in the population, and I^2 indicates the amount of variance observed in the current analyses (Borenstein, 2011). I^2 can be interpreted as low *(I^2 = 0.00–0.49),* moderate *(I^2 = 0.50–0.74),* or considerable *(I^2 > 0.75).* Finally, prediction intervals were calculated to provide an absolute index of dispersion based on the standard deviation (Borenstein, Higgins, Hedges, & Rothstein, 2017).

Sensitivity Analysis Using the total score of the quality of study, a median-split allowed for the articles to be placed into two categories, low quality and high quality. Sensitivity analyses were conducted to determine whether the inclusion of low-quality studies resulted in significant shifts in effect size,

regardless of direction, compared to using only high-quality studies. For domains that yielded a considerable amount of heterogeneity ($I^2 > 75\%$), sensitivity analyses were performed to determine if a single article was responsible for a significant portion of the calculated heterogeneity. As discussed in Borenstein, Hedges, Higgins, and Rothstein (2011), outliers in the data can be found by visually inspecting the forest plots for each domain. A study can be considered an outlier when it has an effect size with confidence intervals that do not overlap with the confidence intervals of the observed summary effect (Viechteauer & Cheung, 2010).

Publication Bias Each neuropsychological domain was assessed for publication bias across studies. Publication bias was analyzed using the Trim and Fill method and visual inspection of the funnel plots. The Trim and Fill method calculates the estimated number of potential missing studies (e.g., unpublished or not included in this analysis; Borenstein, 2011). Estimated study values are then included in the analyses, creating a corrected adjusted effect. As described above, publication bias was also addressed by considering grey literature (e.g., dissertations) and conducting quality of study assessments for each study.

Results

Included Studies and Neuropsychological Domains

A total of 33 studies that investigated the neuropsychological functioning of individuals with heart failure, compared to those without, met inclusion criteria (Table 1). Overall, 20 neuropsychological domains were available for analysis and their effect sizes were calculated (Table 2). All effect sizes were statistically significant, except for simple motor functioning and confrontation naming. The effect sizes ranged from small to medium, with variable heterogeneity across domains. A study conducted by Adebayo and colleagues (2016) was removed in the process of inspecting the forest plots for outliers as it had confidence intervals that did not overlap with the summary effect (Viechteauer & Cheung, 2010). The results presented in the following tables are meant to complement one another and to serve as a roadmap for both researchers and clinicians. Specifically, Table 1 presents study and sample characteristics. The domains extracted from each study are also included in Table 1. Table 2 presents effect sizes for all the domains that were examined in rank order, from the lowest to the highest. Finally, Tables 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13 and 14 provide micro-level data of all effect sizes associated with the tests and subtests that were examined in the neuropsychological literature covered by this meta-analysis.

Global cognition (Table 3) was assessed in 22 studies which yielded a summary effect size of 0.628 (all effect sizes are reported as Hedges' g). Four subdomains of executive functioning were also assessed and their effect sizes ranged from 0.401 to 0.680. Details of significance level and heterogeneity are presented in Table 4. Working memory (Table 5) was assessed in 16 studies and yielded a summary effect size of 0.339. Tables 6 and 7 represent data from articles that studied verbal memory. The effect sizes of all subdomains of verbal memory ranged from 0.518 to 0.596. Moreover, visual memory effect sizes (Table 8) ranged from 0.383 to 0.438. The two language domains (Table 9) ranged from a non-statistically significant 0.164 for confrontation naming to a statistically significant 0.607 for verbal fluency. Processing speed and complex psychomotor speed yielded effect sizes of 0.506 and 0.634, respectively (Table 10). Nine studies were used to evaluate visuospatial construction (Table 11) which yielded a summary effect size of 0.427. The attention (Table 12) and orientation (Table 13) domains yielded small summary effect sizes of 0.278 and 0.277, respectively. Finally, simple motor functioning (Table 14) yielded a non-statistically significant effect size of 0.322.

Secondary Analyses

Sensitivity Analysis The quality of study measure yielded a median total score of 13.5 and a mean score of 13.65 out of 22. Sensitivity analyses were conducted for each domain by removing the articles with a total score less than the median. Three domains were no longer significant after lower quality articles were removed. The executive function-abstraction domain originally had six articles with a $g = 0.401$ ($p = 0.017$). Removing the lower quality articles resulted in three articles with a $g = 0.139$ ($p = 0.521$). The orientation domain originally had four articles with a $g = 0.277$ ($p = 0.031$). Removing the lower quality studies resulted in three articles with a $g = 0.151$ ($p = 0.327$). The visuospatial construction domain originally had nine articles with a $g = 0.427$ ($p < 0.001$). Removing the lower quality studies resulted in six articles with a $g = 0.370$ ($p = 0.058$). The effect sizes for simple motor functioning $g = 0.332$ ($p = 0.102$) and language-confrontation naming $g = 0.360$ ($p = 0.649$) remained insignificant after removal of the lower quality studies. All of the remaining domains with significant effect sizes remained significant following the removal of lower quality studies.

Moreover, sensitivity analyses allowed for the detection of outliers which were significantly contributing to the amount of heterogeneity at both the domain- and test-level. The removal of the study by Moryś, Pąchalska, Bellwon, and Gruchała (2016) resulted in a decrease in heterogeneity from the considerable range ($I^2 > 75\%$) to the moderate ($I^2 = 50$–74.9%) or low range ($I^2 < 49.9\%$). At the domain-level, the original results (i.e., Moryś and colleagues included) and adjusted (i.e.,

Table 2 Effect size data for each domain, in order from smallest effect size to largest

Cognitive Domain	Studies Included and Sample Size				Effect Size Estimates				Prediction Interval (95%)	
	k	*Total Sample*	*Heart Failure*	*Control Group*	*g*	*SE*	*95% CI*	*p*	*Lower Limit*	*Upper Limit*
*Language-Naming**	*3*	435	308	127	0.164	0.360	−0.541 - 0.869	0.649	–	–
Orientation	*4*	203	112	91	0.277	0.129	0.025–0.529	0.031	−0.276	0.830
Attention	*14*	3031	1156	1875	0.278	0.063	0.154–0.402	0.000	−0.073	0.629
*Simple Motor**	*2*	213	125	88	0.332	0.203	−0.066 - 0.730	0.102	–	–
Working Memory	*16*	3323	1344	1979	0.339	0.075	0.192–0.487	0.000	−0.198	0.876
Visual Memory-Delayed	*6*	1414	487	927	0.383	0.067	0.252–0.515	0.000	0.196	0.570
EF-Abstraction	*6*	3022	345	2677	0.401	0.168	0.073–0.730	0.017	−0.668	1.470
Visuospatial Construction	*9*	1691	635	1056	0.427	0.115	0.201–0.654	0.000	−0.284	1.138
Visual Memory-IR	*6*	1206	300	906	0.438	0.075	0.291–0.585	0.000	0.196	0.680
Processing Speed	*11*	1398	720	678	0.506	0.087	0.335–0.677	0.000	−0.028	1.040
Verbal Memory-IR	*17*	6480	1600	4880	0.518	0.062	0.396–0.640	0.000	0.062	0.975
Verbal Memory-Brief Screener	*7*	2990	306	2684	0.560	0.190	0.188–0.932	0.003	−0.651	1.771
Verbal Memory-Recognition	*4*	306	154	152	0.568	0.162	0.250–0.886	0.000	−0.674	1.810
Verbal Memory-Delayed Recall	*14*	3126	1325	1801	0.596	0.116	0.368–0.824	0.000	−0.304	1.496
Language-Fluency/Initiation	*10*	2604	1044	1560	0.607	0.104	0.404–0.810	0.000	−0.080	1.294
Global Cognition	*22*	4036	1643	2393	0.628	0.079	0.472–0.783	0.000	−0.029	1.285
EF-Planning	*3*	505	154	351	0.631	0.106	0.423–0.838	0.000	−0.711	1.973
Complex Psychomotor	*7*	4243	701	3542	0.634	0.085	0.466–0.801	0.000	0.138	1.130
EF-Cognitive Flexibility	*12*	1445	772	673	0.660	0.084	0.496–0.823	0.000	0.193	1.127
EF-Inhibition	*7*	463	241	222	0.680	0.116	0.452–0.908	0.000	0.150	1.210

Note. *CI* confidence interval, *EF* executive function, *g* Hedges' g, *k* number of studies, *SE* standard error, *IR immediate recall*

* Language-naming and simple motor were the only two domains that did not have a significant effect size ($p < 0.05$)

Table 3 Global cognition effect size data and degree of heterogeneity

Domain, Test, and Outcome	*k*	Total *(n)*	Effect Size Estimates						Heterogeneity				
			g	*SE*	*95% CI*		*z*	*p*	*Q*	*df*	I^2	Tau^2	*p*
					Lower	Upper							
Global Cognition	**22**	**4036**	**0.628**	**0.079**	**0.472**	**0.783**	**7.922**	**0.000**	**91.245**	**21**	**76.985**	**0.093**	**0.000**
MMSE-Total Score	13	3151	0.630	0.101	0.432	0.828	6.241	0.000	58.961	12	79.648	0.096	0.000
CAMCOG-Total Score	4	334	0.927	0.196	0.543	1.312	4.730	0.000	8.760	3	65.752	0.115	0.033
MoCA-Total Score	3	235	0.836	0.228	0.390	1.282	3.672	0.000	0.205	2	0.000	0.000	0.903
ACE-R-Total Score	1	59	0.520	0.397	−0.258	1.298	1.310	0.190					
DRS-Total Score	1	75	0.393	0.378	−0.348	1.133	1.039	0.299					
Mini-Cog-Total Score	1	241	0.121	0.325	−0.517	0.759	0.371	0.711					
RBANS-Total Score	1	62	0.148	0.390	−0.617	0.913	0.379	0.705					

Note. *ACE-R* Addenbrooke's Cognitive Examination-R, *CAMCOG* Cambridge Cognition Examination, *CI* confidence interval, *df* degrees of freedom, *DRS* Dementia Rating Scale, *EF* executive function, *g* Hedges' g, *k* number of studies, *MMSE* Mini Mental Status Examination, *MoCA* Montreal Cognitive Assessment, *n* sample size, *RBANS* Repeatable Battery for the Assessment of Neuropsychological Status, *SE* standard error

Table 4 Executive function effect size data and degree of heterogeneity

Domain, Test, and Outcome	*k*	Total *(n)*	Effect Size Estimates						Heterogeneity				
			g	*SE*	***95% CI***		*z*	*p*	*Q*	*df*	I^2	Tau^2	*p*
					Lower	Upper							
EF-Abstraction	**6**	**3022**	**0.401**	**0.168**	**0.073**	**0.730**	**2.393**	**0.017**	**23.786**	**5**	**78.979**	**0.120**	**0.000**
CAMCOG-Abstraction	2	121	0.735	0.457	−0.160	1.631	1.609	0.108	5.329	1	81.234	0.340	0.021
Short Category Test	1	113	0.230	0.616	−0.977	1.437	0.373	0.709					
DRS-Conceptualization	1	75	−0.202	0.626	−1.430	1.025	−0.323	0.747					
Letter Series	1	2671	0.154	0.589	−1.001	1.309	0.261	0.794					
Letter Set	1	2671	0.164	0.589	−0.991	1.320	0.279	0.780					
MoCA-Abstraction	1	42	0.488	0.660	−0.805	1.780	0.739	0.460					
SILS-Abstraction	1	113	0.925	0.619	−0.287	2.137	1.495	0.135					
Word Series	1	2671	0.218	0.589	−0.937	1.373	0.370	0.712					
EF-Cognitive Flexibility	**12**	**1445**	**0.660**	**0.084**	**0.496**	**0.823**	**7.900**	**0.000**	**20.859**	**11**	**47.265**	**0.037**	**0.035**
Trail Making Test Part-B	10	1290	0.631	0.080	0.474	0.788	7.884	0.000	12.801	9	29.695	0.018	0.172
*Intra-Extra Dimensional Set Shifting**	1	104	0.470	0.242	−0.005	0.945	1.940	0.052					
Color Trails Test-2 (CTT-2)	1	100	1.206	0.255	0.706	1.706	4.731	0.000					
Trail Making Test (B-A)	1	55	0.397	0.301	−0.193	0.987	1.319	0.187					
EF-Inhibition	**7**	**463**	**0.680**	**0.116**	**0.452**	**0.908**	**5.844**	**0.000**	**8.714**	**6**	**31.145**	**0.029**	**0.190**
Stroop-Interference Score	5	362	0.602	0.107	0.392	0.812	5.618	0.000	3.482	4	0.000	0.000	0.481
Hayling Sentence Completion	1	54	1.320	0.297	0.738	1.902	4.446	0.000					
Response Inhibition Test	1	47	0.609	0.294	0.034	1.185	2.075	0.038					
EF-Planning	**3**	**505**	**0.631**	**0.106**	**0.423**	**0.838**	**5.964**	**0.000**	**1.264**	**2**	**0.000**	**0.000**	**0.532**
*Stockings of Cambridge**	1	104	0.510	0.202	0.115	0.905	2.531	0.011					
Clock Drawing Test	1	354	0.728	0.137	0.459	0.997	5.298	0.000					
Tower of London	1	47	0.446	0.291	−0.124	1.015	1.534	0.125					

Note. *Both tests were components of the Cambridge Neuropsychological Test Automated Battery (CANTAB). *CAMCOG* Cambridge Cognition Examination, *CI* confidence interval, *df* degrees of freedom, *DRS* Dementia Rating Scale, *EF* executive function, *g* Hedges' g, *k* number of studies, *MMSE* Mini Mental Status Examination, *MoCA* Montreal Cognitive Assessment, *n* sample size, *RBANS* Repeatable Battery for the Assessment of Neuropsychological Status, *SE* standard error, *SILS* Shipley Institute of Living Scale

Moryś and colleagues excluded) were (a) global cognition original ($k = 21$, $g = 0.628$, $p < 0.001$; $I^2 = 76.985\%$, $p < 0.001$) and adjusted ($k = 20$, $g = 0.584$, $p < 0.001$; $I^2 = 73.345\%$, $p < 0.001$), (b) verbal memory-delayed recall original ($k = 14$, $g = 0.596$, $p < 0.001$; $I^2 = 88.156\%$, $p < 0.001$) and adjusted ($k = 13$, $g = 0.490$, $p < 0.001$; $I^2 = 72.903\%$, $p < 0.001$), and (c) verbal fluency original ($k = 10$, $g = 0.607$, $p < 0.001$; $I^2 = 80.772\%$, $p < 0.001$) and adjusted ($k = 9$, $g = 0.492$, $p < 0.001$; $I^2 = 51.511\%$, $p = 0.036$).

At the test-level, the original and adjusted effect sizes and heterogeneity included (a) WMS-Logical Memory-immediate recall original ($k = 3$, $g = 0.615$, $p < 0.001$; $I^2 = 93.016\%$, $p < 0.001$) and adjusted ($k = 2$, $g = 0.251$, $p = 0.008$; $I^2 = 0.000\%$, $p = 0.833$), (b) CVLT-delayed recall original ($k = 3$, $g = 1.137$, $p < 0.001$; $I^2 = 78.961$, $p < 0.001$) and adjusted ($k = 2$, $g = 0.908$, $p < 0.001$; $I^2 = 0.000\%$, $p = 0.356$), (c) WMS-Logical Memory-delayed recall original ($k = 3$, $g = 0.694$, $p < 0.001$; $I^2 = 94.740\%$, $p < 0.001$) and adjusted ($k = 2$, $g = 0.238$, $p = 0.053$; $I^2 = 0.000\%$, $p = 0.685$), (d) semantic fluency original ($k = 4$, $g = 0.702$, $p = 0.001$; $I^2 = 89.437\%$, $p < 0.001$) and adjusted ($k = 3$, $g = 0.387$, $p < 0.001$; $I^2 = 4.120\%$, $p = 0.352$), and (e) MMSE-total score original ($k = 13$, $g = 0.630$, $p < 0.001$; $I^2 = 79.648\%$, $p < 0.001$) and adjusted ($k = 12$, $g = 0.558$, $p < 0.001$; $I^2 = 72.393\%$, $p < 0.001$). Following the removal of Almeida et al. (2001), the heterogeneity significantly lowered in executive function-abstraction (original: $k = 6$, $g = 0.401$, $p = 0.017$; $I^2 = 78.979\%$, $p < 0.001$; adjusted: $k = 5$, $g = 0.261$, $p = 0.049$; $I^2 = 61.485\%$, $p = 0.034$).

Following the removal of Alwerdt, Edwards, Athilingam, O'Connor, and Valdes (2013), the heterogeneity in the domain

Table 5 Working memory effect size data and degree of heterogeneity

Domain, Test, and Outcome	*k*	Total *(n)*	Effect Size Estimates						Heterogeneity				
			g	*SE*	*95% CI*		*z*	*p*	*Q*	*df*	I^2	Tau^2	*p*
					Lower	Upper							
Working Memory	**16**	**3323**	**0.339**	**0.075**	**0.192**	**0.487**	**4.502**	**0.000**	**56.758**	**15**	**73.572**	**0.057**	**0.000**
Digit Span-Backward	7	2140	0.321	0.076	0.172	0.471	4.205	0.000	7.069	6	15.125	0.004	0.314
Digit Span-Total Score	5	593	0.374	0.110	0.159	0.589	3.409	0.001	7.570	4	47.159	0.042	0.109
CDR Quality of Working Memory	1	76	0.000	0.256	−0.502	0.502	0.000	1.000					
Cogstate One-Back Test	1	140	0.613	0.209	0.203	1.023	2.930	0.003					
Corsi's Span	1	515	0.000	0.140	−0.275	0.275	0.000	1.000					
N-Back Verbal Test-Errors	1	47	0.000	0.310	−0.608	0.608	0.000	1.000					
N-Back Verbal Test-Omissions	1	47	0.508	0.315	−0.109	1.124	1.613	0.107					
PASAT-Total Number Incorrect	1	102	0.507	0.273	−0.027	1.041	1.860	0.063					
Spatial Span Backward	1	100	0.781	0.238	0.315	1.246	3.287	0.001					
WAIS-Letter Number Sequencing	1	62	0.215	0.278	−0.330	0.760	0.774	0.439					
Verbal Word Span	1	515	−0.089	0.140	−0.364	0.186	−0.636	0.525					

Note. *CDR* Cognitive Drug Research, *CI* confidence interval, *df* degrees of freedom, *EF* executive function, *g* Hedges' g, *k* number of studies, *n* sample size, *PASAT* Paced Auditory Serial Addition Test, *SE* standard error, *WAIS* Wechsler Adult Intelligence Scale

memory-brief screening significantly lowered (original: $k = 7$, $g = 0.560$, $p = 0.003$; $I^2 = 79.498\%$, $p < 0.001$; adjusted: $k = 6$, $g = 0.669$, $p < 0.001$; $I^2 = 44.307\%$, $p = 0.110$) and the heterogeneity yielded by the test HVLT-immediate recall also lowered (original: $k = 3$, $g = 0.384$, $p = 0.029$; $I^2 = 81.914\%$, $p = 0.004$; adjusted: $k = 2$, $g = 0.527$, $p = 0.047$; $I^2 = 60.142\%$, $p = 0.113$). Moreover, there was a considerable amount of heterogeneity in the language- confrontation naming domain. This domain consisted of three different confrontation naming tests that were measured in a single study and the effect sizes were significantly different than one another, which likely contributed to the considerable heterogeneity.

Publication Bias across Studies As measured by the Trim and Fill method, publication bias across studies was assessed for each neuropsychological domain. Among the 20 domains analyzed, possible overestimation of effect size was observed in complex psychomotor speed, global cognition, visual memory-immediate recall, visual memory-delayed recall, and working memory (Fig. 2). The observed and adjusted effects sizes included: (a) complex psychomotor speed observed ($g = 0.634$) and adjusted ($g = 0.575$), (b) global cognition observed ($g = 0.628$) and adjusted ($g = 0.463$), (c) visual memory-immediate recall observed ($g = 0.438$) and adjusted ($g = 0.408$), (d) visual memory-delayed recall observed ($g = 0.383$) and adjusted ($g = 0.369$), and (e) working memory observed ($g = 0.339$) and adjusted ($g = 0.219$).

Discussion

This meta-analysis quantitatively synthesized available studies that examined the neuropsychological performance of patients with heart failure. After screening 9741 articles, 33 met inclusion criteria and provided data for the calculation of effect sizes across 20 cognitive domains which were analyzed independently. In 18 out of the 20 domains analyzed, individuals in the heart failure group exhibited significantly lowered neuropsychological performance compared to controls, suggesting diffuse cognitive difficulties. The largest effect sizes were most evident in global cognition, executive functioning, complex psychomotor speed, and verbal memory. Prior research has identified low cardiac output and poor systemic oxygenation as being associated with generalized structural brain changes in this population (Kumar et al., 2015; Woo et al., 2015b). Therefore, it is possible that the overall diffuse changes in function might be explained by low blood flow in the watershed areas and generalized hypoxia (de la Torre, 2012; Lezak et al., 2012; Parsons & Hammeke, 2014).

Other evidence for potential structural changes that may explain our findings come from neuroimaging research. Specifically, neuroimaging studies have found structural changes associated with heart failure using regional and whole-brain analyses (Frey et al., 2018; Kumar et al., 2015; Meguro, Meguro, & Kunieda, 2017; Niizeki,

Table 6 Verbal memory effect size data and degree of heterogeneity

Domain, Test, and Outcome	*k*	Total *(n)*	Effect Size Estimates						Heterogeneity				
			g	*SE*	*95% CI*		*z*	*p*	*Q*	*df*	I^2	Tau^2	*p*
					Lower	Upper							
Verbal Memory-Immediate	**17**	**6480**	**0.518**	**0.062**	**0.396**	**0.640**	**8.332**	**0.000**	**57.684**	**16**	**72.263**	**0.042**	**0.000**
RAVLT-Immediate Recall	5	3444	0.479	0.146	0.192	0.766	3.275	0.001	4.197	4	4.696	0.001	0.380
HVLT-Immediate Recall	3	3337	0.384	0.176	0.039	0.730	2.179	0.029	11.058	2	81.914	0.066	0.004
CVLT-Immediate Total Recall	3	313	0.972	0.205	0.571	1.374	4.748	0.000	2.735	2	26.862	0.017	0.255
CVLT-Short Delay Free Recall	3	313	0.887	0.234	0.429	1.346	3.793	0.000	7.034	2	71.568	0.116	0.030
WMS-Logical Memory Immediate	3	1054	0.615	0.191	0.240	0.990	3.216	0.001	28.637	2	93.016	0.401	0.000
CAB Text Recall Test-Immediate Recall	1	81	0.567	0.359	−0.136	1.270	1.581	0.114					
CERAD Word List Learning-1-3 Recall	1	841	0.300	0.300	−0.287	0.888	1.001	0.317					
Cogstate - ISDL-Total Recall	1	140	0.618	0.329	−0.026	1.262	1.881	0.060					
CVLT-Short Delay Cued Recall	1	100	1.407	0.357	0.707	2.107	3.941	0.000					
DRS-Memory	1	75	0.399	0.363	−0.312	1.110	1.100	0.271					
Prose Recall Test	1	606	0.331	0.301	−0.259	0.921	1.098	0.272					
RVLT-Brief Delay Recall	1	100	0.591	0.345	−0.086	1.268	1.712	0.087					
SVLT-Immediate Recall	1	201	0.489	0.315	−0.128	1.106	1.552	0.121					
Verbal Memory-Delayed	**14**	**3126**	**0.596**	**0.116**	**0.368**	**0.824**	**5.126**	**0.000**	**109.761**	**13**	**88.156**	**0.157**	**0.000**
RAVLT-Delayed Recall	4	771	0.379	0.226	−0.063	0.822	1.680	0.093	1.268	3	0.000	0.000	0.737
WMS-Logical Memory Delayed Recall	3	1054	0.694	0.258	0.187	1.200	2.685	0.007	38.023	2	94.740	0.556	0.000
CVLT-Long Delayed Free Recall	3	313	1.137	0.269	0.610	1.665	4.224	0.000	9.506	2	78.961	0.184	0.009
HVLT-Delayed Recall	2	666	0.377	0.305	−0.220	0.974	1.237	0.216	2.554	1	60.839	0.030	0.110
CAB Text Recall Test-Delayed Recall	1	81	1.025	0.471	0.102	1.947	2.178	0.029					
CERAD-Delayed List Learning	1	841	0.044	0.422	−0.784	0.871	0.103	0.918					
Cogstate ISDL-Delayed Recall	1	140	0.614	0.443	−0.255	1.482	1.385	0.166					
SVLT-Delayed Recall	1	201	0.756	0.434	−0.094	1.607	1.744	0.081					
Verbal Memory-Recognition	**4**	**306**	**0.568**	**0.162**	**0.250**	**0.886**	**3.498**	**0.000**	**6.717**	**3**	**55.338**	**0.057**	**0.081**
CVLT-Recognition	2	155	0.693	0.164	0.371	1.016	4.216	0.000	0.577	1	0.000	0.000	0.447
RAVLT- Recognition	2	151	0.343	0.163	0.024	0.662	2.105	0.035	0.861	1	0.000	0.000	0.353
WMS Logical Memory II-Recognition	1	100	0.953	0.210	0.542	1.363	4.546	0.000					

Note. *CAB* Cognitive Assessment Battery, *CERAD* Consortium to Establish a Registry for Alzheimer's Disease, *CI* confidence interval, *df* degrees of freedom, *DRS* Dementia Rating Scale, *g* Hedges' g, *HVLT* Hopkins Verbal Learning Test; *ISDL* International Shopping List, *k* number of studies, *n* sample size, *RAVLT* Rey Auditory Verbal Learning Test, *SE* standard error, *SVLT* Seoul Verbal Learning Test, *WMS* Wechsler Memory Scale

Iwayama, Ikeno, & Watanabe, 2019; Siachos et al., 2005; Woo et al., 2015b). Across several magnetic resonance imaging (MRI) studies, atrophy in the medial temporal lobe has been consistently observed in those with heart failure (Frey et al., 2018; Meguro et al., 2017; Woo et al., 2015a). Bilateral neuronal loss in the insula, with greater right hemisphere involvement, has also been found in this population (Woo et al., 2014). Atrophy in the medial temporal lobe, particularly in the hippocampus, has been associated with heart failure severity, verbal memory impairment, as well as an increased risk for rehospitalization and mortality (Frey et al., 2018; Niizeki et al., 2019).

Between MRI studies, there have been inconsistent findings related to the potential existence of diffuse structural changes in those with heart failure. For instance, Kumar et al. (2015) conducted a neuroimaging study and found significant cortical atrophy in the frontal, parietal, temporal, and occipital lobe, with more left hemisphere involvement. Meguro et al. (2017) and Woo et al. (2015a) conducted a similar study and did not find significant whole-brain differences between those with heart failure and those without the condition. However, a diffusion tensor imaging (DTI) study found increased global and regional mean diffusivity in those with heart failure, which is suggestive of chronic tissue

Table 7 Verbal memory brief screening effect size data and degree of heterogeneity

Domain, Test, and Outcome	*k*	Total *(n)*	Effect Size Estimates						Heterogeneity				
			g	*SE*	*95% CI*		*z*	*p*	*Q*	*df*	I^2	Tau^2	*p*
					Lower	Upper							
Verbal Memory-Brief Screening	**7**	**2990**	**0.560**	**0.190**	**0.188**	**0.932**	**2.952**	**0.003**	**29.265**	**6**	**79.498**	**0.186**	**0.000**
CAMCOG-Memory	2	121	0.874	0.221	0.442	1.307	3.963	0.000	1.353	1	26.093	0.026	0.245
CDR Quality of Episodic Memory	1	76	0.243	0.674	−1.078	1.564	0.361	0.718					
MoCA-Memory	1	42	1.069	0.713	−0.328	2.467	1.500	0.134					
RBMT-Story Recall Composite	1	2671	0.000	0.640	−1.255	1.255	0.000	1.000					
RBMT-Delivering message	1	40	0.000	0.706	−1.383	1.383	0.000	1.000					
RBMT-Remembering appointment	1	40	0.408	0.707	−0.978	1.794	0.577	0.564					
RBMT-Remembering belonging	1	40	0.347	0.707	−1.038	1.733	0.492	0.623					
RBMT-Story Delayed recall	1	40	0.225	0.706	−1.159	1.609	0.318	0.750					
RBMT-Story Immediate recall	1	40	0.665	0.710	−0.726	2.056	0.937	0.349					
LGT-3 Verbal Memory	1	40	0.776	0.711	−0.617	2.170	1.092	0.275					

Note. *CAMCOG* Cambridge Cognition Examination, *CDR* Cognitive Drug Research, *CI* confidence interval, *df* degrees of freedom, *g* Hedges' g, *k* number of studies, *n* sample size, *LGT* Baeumlet's Lernund Gedachtnishest LGT-3, *RBMT* Rivermead Behavioral Memory Test, *SE* standard error

Table 8 Visual memory effect size data and degree of heterogeneity

Domain, Test, and Outcome	*k*	Total *(n)*	Effect Size Estimates						Heterogeneity				
			g	*SE*	*95% CI*		*z*	*p*	*Q*	*df*	I^2	Tau^2	*p*
					Lower	Upper							
Visual Memory-Immediate	**6**	**1206**	**0.438**	**0.075**	**0.291**	**0.585**	**5.847**	**0.000**	**5.238**	**5**	**4.550**	**0.002**	**0.387**
BVMT-R-Total Recall	1	55	0.575	0.274	0.039	1.111	2.102	0.036					
RBMT-Route-Immediate recall	1	40	−0.192	0.311	−0.801	0.417	−0.618	0.537					
Thurstone's Pictures	1	606	0.428	0.112	0.208	0.648	3.811	0.000					
Rey Figure-Immediate Recall	1	354	0.495	0.136	0.229	0.762	3.644	0.000					
FGT-Learning Sum	1	47	0.683	0.295	0.104	1.262	2.312	0.021					
CANTAB-Pattern Recognition	1	104	0.430	0.201	0.037	0.823	2.145	0.032					
Visual Memory-Delayed	**6**	**1414**	**0.383**	**0.067**	**0.252**	**0.515**	**5.712**	**0.000**	**3.556**	**5**	**0.000**	**0.000**	**0.615**
BVMT-Delayed Recall	1	55	0.617	0.274	0.079	1.155	2.248	0.025					
FGT-Delayed Free Reproduction II	1	47	0.535	0.292	−0.038	1.107	1.830	0.067					
Figure Copy and Figure Memory-Recall	1	312	0.304	0.141	0.027	0.581	2.153	0.031					
Memory-In-Reality	1	606	0.330	0.112	0.111	0.550	2.949	0.003					
RBMT-Composite	1	40	0.094	0.277	−0.450	0.638	0.339	0.735					
Rey Figure-Delayed Recall	1	354	0.515	0.136	0.248	0.782	3.786	0.000					

Note. *BVMT* Brief Visuospatial Memory Test, *CAN-TAB* Cambridge Neuropsychological Test Automated Battery, *CI* confidence interval, *df* degrees of freedom, *FGT* Figural Memory Test, *g* Hedges' g, *k* number of studies, *n* sample size, *RBMT* Rivermead Behavioral Memory Test, *Rey Figure* Modified Rey-Osterrieth Complex Figure Test, *SE* standard error

Table 9 Language effect size data and degree of heterogeneity

Domain, Test, and Outcome	*k*	Total *(n)*	Effect Size Estimates						Heterogeneity				
			g	*SE*	*95% CI*		*z*	*p*	*Q*	*df*	I^2	Tau^2	*p*
					Lower	Upper							
Language-Naming	**3**	**435**	**0.164**	**0.360**	**−0.541**	**0.869**	**0.456**	**0.649**	**15.988**	**2**	**87.490**	**0.334**	**0.000**
Boston Naming Test	1	312	0.054	0.228	−0.394	0.502	0.236	0.813					
CAB-Naming	1	81	0.910	0.293	0.335	1.484	3.102	0.002					
MoCA-Naming	1	42	−0.529	0.358	−1.231	0.173	−1.478	0.140					
Language-Fluency Initiation	**10**	**2604**	**0.607**	**0.104**	**0.404**	**0.810**	**5.862**	**0.000**	**46.807**	**9**	**80.772**	**0.078**	**0.000**
Phonemic Fluency	8	2029	0.613	0.147	0.325	0.900	4.179	0.000	19.471	7	64.049	0.049	0.007
Semantic Fluency	4	1073	0.702	0.203	0.305	1.100	3.466	0.001	28.402	3	89.437	0.174	0.000
Combined Fluency	2	160	1.346	0.318	0.723	1.968	4.236	0.000	20.419	1	95.103	1.259	0.000

Note. *CAB* Cognitive Assessment Battery, *CI* confidence interval, *df* degrees of freedom, *g* Hedges' g, *k* number of studies, *MoCA* Montreal Cognitive Assessment, *n* sample size, *SE* standard error

damage (Woo et al., 2015b). This damage was present in areas such as the limbic system, basal ganglia, thalamus, solitary tract nucleus, and frontal lobes.

Although there are mixed findings related to diffuse atrophy, the literature consistently supports that those with heart failure are at a significantly higher risk of undetected ischemic stroke (Frey et al., 2018; Siachos et al., 2005). One study found that 34% of those with heart failure had neuroimaging findings that were consistent with an ischemic stroke, despite presenting neurologically asymptomatic (Siachos et al., 2005). Likewise, Frey et al. (2018) had similar findings and reported that those with heart failure were at a 2.7-fold increased risk for having undetected silent lacunes and a 3.54-fold increased risk for silent brain infarctions. In sum, the neuroimaging literature collectively supports the negative impact that heart failure has on the integrity of the brain, although the mechanism of action remains unclear. Some studies

Table 10 Processing speed and complex psychomotor speed data and degree of heterogeneity

Domain, Test, and Outcome	*k*	Total *(n)*	Effect Size Estimates						Heterogeneity				
			g	*SE*	*95% CI*		*z*	*p*	*Q*	*df*	I^2	Tau^2	*p*
					Lower	Upper							
Processing Speed	**11**	**1398**	**0.506**	**0.087**	**0.335**	**0.677**	**5.807**	**0.000**	**24.663**	**10**	**59.454**	**0.048**	**0.006**
Trail Making Test Part- A	10	1298	0.477	0.102	0.277	0.677	4.681	0.000	21.569	9	58.274	0.057	0.010
Stroop Reading	4	281	0.440	0.164	0.027	0.119	2.685	0.007	2.955	3	0.000	0.000	0.399
Color Trails Test-I	1	100	0.967	0.318	0.343	1.591	3.037	0.002					
Complex Psychomotor	**7**	**4243**	**0.634**	**0.085**	**0.466**	**0.801**	**7.412**	**0.000**	**15.925**	**6**	**62.324**	**0.030**	**0.014**
WAIS-Digit Symbol Substitution	4	3904	0.512	0.063	0.388	0.635	8.132	0.000	3.339	3	10.149	0.002	0.342
Symbol Digit Modalities Test	2	181	1.079	0.160	0.765	1.393	6.739	0.000	0.917	1	0.000	0.000	0.338
Letter Cancellation Test	1	80	0.693	0.238	0.227	1.159	2.914	0.004					
WAIS-Digit Coding	1	158	0.560	0.165	0.236	0.884	3.388	0.001					
WAIS-Digit Copying	1	158	0.432	0.164	0.110	0.754	2.633	0.008					

Note. *CI* confidence interval, *df* degrees of freedom, *g* Hedges' g, *k* number of studies, *n* sample size, *SE* standard error, *WAIS* Wechsler Adult Intelligence Scale

Table 11 Visuospatial effect size data and degree of heterogeneity

Domain, Test, and Outcome	*k*	Total *(n)*	Effect Size Estimates						Heterogeneity				
			g	*SE*	*95% CI*		*z*	*p*	*Q*	*df*	I^2	Tau^2	*p*
					Lower	Upper							
Visuospatial Construction	**9**	**1691**	**0.427**	**0.115**	**0.201**	**0.654**	**3.701**	**0.000**	**26.203**	**8**	**69.469**	**0.077**	**0.001**
Block Design	2	661	0.574	0.164	0.253	0.895	3.509	0.000	1.520	1	34.196	0.024	0.218
CAB-Clocks and Cube	1	81	0.785	0.276	0.245	1.325	2.850	0.004					
DRS-Construction	1	75	−0.211	0.276	−0.752	0.331	−0.762	0.446					
Figure Copy and Figure Memory-Copy	1	312	0.205	0.209	−0.204	0.614	0.981	0.326					
Fragmented Line Drawings	1	104	0.955	0.260	0.447	1.464	3.681	0.000					
MoCA-Visuospatial	1	42	0.589	0.347	−0.091	1.268	1.697	0.090					
RBANS-Visuospatial Index	1	62	−0.101	0.294	−0.678	0.476	−0.344	0.731					
Rey Figure-Copy	1	354	0.395	0.205	−0.006	0.797	1.929	0.054					

Note. *CAB* Cognitive Assessment Battery, *CI* confidence interval, *df* degrees of freedom, *DRS* Dementia Rating Scale, *g* Hedges' g, *k* number of studies, *MoCA* Montreal Cognitive Assessment, *n* sample size, *RBANS* Repeatable Battery for the Assessment of Neuropsychological Status, *Rey Figure* Modified Rey-Osterrieth Complex Figure Test, *SE* standard error, *WAIS* Wechsler Adult Intelligence Scale

support a generalized diffuse ischemic or structural changes while others seem to present more regional alterations.

In the current meta-analysis, individuals with heart failure demonstrated significantly reduced performance on tests of global cognition that were most commonly evaluated by the MMSE, MoCA, and the Cambridge Cognitive Examination (CAMCOG). All three tests yielded comparable effect sizes, with the CAMCOG having the largest ($g = 0.927$), followed by the MoCA ($g = 0.836$) and MMSE ($g = 0.630$). Interestingly, when studies that only reported the MMSE as the sole neurocognitive measure (typically for screening purposes) were removed, the effect size for the MMSE increased to $g = 0.720$. Post hoc subgroup analyses statistically examining these three commonly used tests were not significant. These findings support the fact that all three instruments result in similar outcomes when screening for cognitive changes associated with heart failure. Although cognitive screeners are useful in detecting changes in global cognition, a comprehensive neuropsychological assessment may be required

Table 12 Attention effect size data and degree of heterogeneity

Domain, Test, and Outcome	*k*	Total *(n)*	Effect Size Estimates						Heterogeneity				
			g	*SE*	*95% CI*		*z*	*p*	*Q*	*df*	I^2	Tau^2	*p*
					Lower	Upper							
Attention	**14**	**3031**	**0.278**	**0.063**	**0.154**	**0.402**	**4.385**	**0.000**	**24.480**	**13**	**46.895**	**0.022**	**0.027**
Digit Span-Forward	7	2140	0.267	0.110	0.052	0.483	2.434	0.015	19.309	6	68.927	0.054	0.004
CAMCOG-Attention	2	121	0.376	0.249	−0.112	0.864	1.512	0.131	1.136	1	11.972	0.010	0.287
Attention Matrices	1	515	0.373	0.240	−0.098	0.844	1.553	0.120					
CDR Continuity of Attention	1	76	0.000	0.322	−0.631	0.631	0.000	1.000					
DRS-Attention	1	75	0.229	0.324	−0.406	0.863	0.707	0.479					
MoCA-Attention	1	42	0.347	0.382	−0.402	1.096	0.908	0.364					
RBANS-Attention Index	1	62	0.276	0.340	−0.390	0.942	0.812	0.417					
WMS Spatial Span-Forward	1	100	0.547	0.305	−0.051	1.144	1.794	0.073					

Note. *CAMCOG* Cambridge Cognition Examination, *CDR* Cognitive Drug Research, *CI* confidence interval, *df* degrees of freedom, *DRS* Dementia Rating Scale, *g* Hedges' g, *k* number of studies, *MoCA* Montreal Cognitive Assessment,*n* sample size, *RBANS* Repeatable Battery for the Assessment of Neuropsychological Status, *Rey Figure* Modified Rey-Osterrieth Complex Figure Test, *SE* standard error, *WMS* Wechsler Memory Scale

Table 13 *Orientation effect size data and degree of heterogeneity*

Domain, Test, and Outcome	*k*	Total *(n)*	Effect Size Estimates						Heterogeneity				
			g	*SE*	*95% CI*		*z*	*p*	*Q*	*df*	I^2	Tau^2	*p*
					Lower	Upper							
Orientation	**4**	**203**	**0.277**	**0.129**	**0.025**	**0.529**	**2.152**	**0.031**	**2.945**	**3**	**0.000**	**0.000**	**0.400**
CAMCOG-Orientation	2	121	0.495	0.187	0.129	0.860	2.653	0.008	0.239	1	0.000	0.000	0.625
MoCA-Orientation	1	42	0.000	0.304	−0.596	0.596	0.000	1.000					
RBMT-Orientation	1	40	0.166	0.310	−0.443	0.774	0.533	0.594					
RBMT-Remembering date	1	40	0.074	0.310	−0.534	0.681	0.237	0.813					

Note. *CAMCOG* Cambridge Cognition Examination, *CI* confidence interval, *df* degrees of freedom, *g* Hedges' g, *k* number of studies, *MoCA* Montreal Cognitive Assessment, *n* sample size, *RBMT* Rivermead Behavioral Memory Test, *SE* standard error

when significant neurocognitive decline is suspected or observed in individual patients. These evaluations are particularly useful for individuals when heart failure is associated with other comorbid conditions that are known to impact cognition such as COPD, atrial fibrillation, sleep apnea, or depression (Aldrugh, Sardana, Henninger, Saczynski, & Mcmanus, 2017; Yohannes et al., 2017). The literature supports that these commonly co-occurring disorders can exacerbate cognitive impairment in those with heart failure, negatively impacting self-care practices and quality of life (Alosco et al., 2013; Alosco et al., 2015; Hjelm et al., 2013; Komori et al., 2016).

When conducting assessments in this clinical population, it is critical to assess executive function and memory abilities. The current meta-analysis highlights the fact that the domains of executive function and verbal memory were highly impacted by heart failure. Across the 20 domains in this study, cognitive flexibility and inhibition had the largest effect sizes. The most commonly used tests in these domains were the Trail Making Test-Part B and the Stroop Color-Word Interference. In order to perform in the normal ranges on these two tests, individuals must have intact attention, processing speed, and working memory. These three abilities work simultaneously to allow an individual to cognitively shift between letters and numbers or perceived words versus colors (Suchy, 2015). Along with mental flexibility, these tasks require the inhibition of prepotent responses. Reduced mental flexibility and inhibition may present as concrete thinking and disinhibited behavior in everyday life (Suchy, 2015). At a practical level, executive dysfunction has been associated with greater dependence on caretakers as well as unhealthy behaviors (e.g., cigarette smoking) in individuals with heart failure (Alosco et al., 2014; Harkness et al., 2014).

Previous research has shown that, in addition to the frontal lobe, heart failure is associated with medial temporal lobe structural abnormalities, especially in the hippocampus (Meguro et al., 2017; Nikendei et al., 2019). This is reflected in the current meta-analysis by medium effect sizes found in verbal memory measures of immediate recall ($g = 0.518$), delayed recall ($g = 0.596$), and recognition ($g = 0.568$). In the verbal memory domain, the California Verbal Learning Test (CVLT) had the largest effect sizes among tests that were reported in at least three studies. Interestingly, the overall effect size for the domain that consists of brief, seemingly easier, measures of memory yielded a comparable effect size to more comprehensive measures (approximately $g = 0.560$). However, most tests that contributed to the verbal memory-brief screening domain were included in only one study;

Table 14 Simple motor effect size data and degree of heterogeneity

Domain, Test, and Outcome	*k*	Total *(n)*	Effect Size Estimates						Heterogeneity				
			g	*SE*	*95% CI*		*z*	*p*	*Q*	*df*	I^2	Tau^2	*p*
					Lower	Upper							
Simple Motor	**2**	**213**	**0.332**	**0.203**	**−0.066**	**0.730**	**1.635**	**0.102**	**4.121**	**1**	**75.733**	**0.062**	**0.042**
Finger Tapping	1	100	0.129	0.141	−0.148	0.406	0.912	0.362					
Grooved Pegboard	1	113	0.535	0.141	0.258	0.812	3.783	0.000					

Note. *CI* confidence interval, *df* degrees of freedom, *g* Hedges' g, *k* number of studies, *n* sample size, *SE* standard error

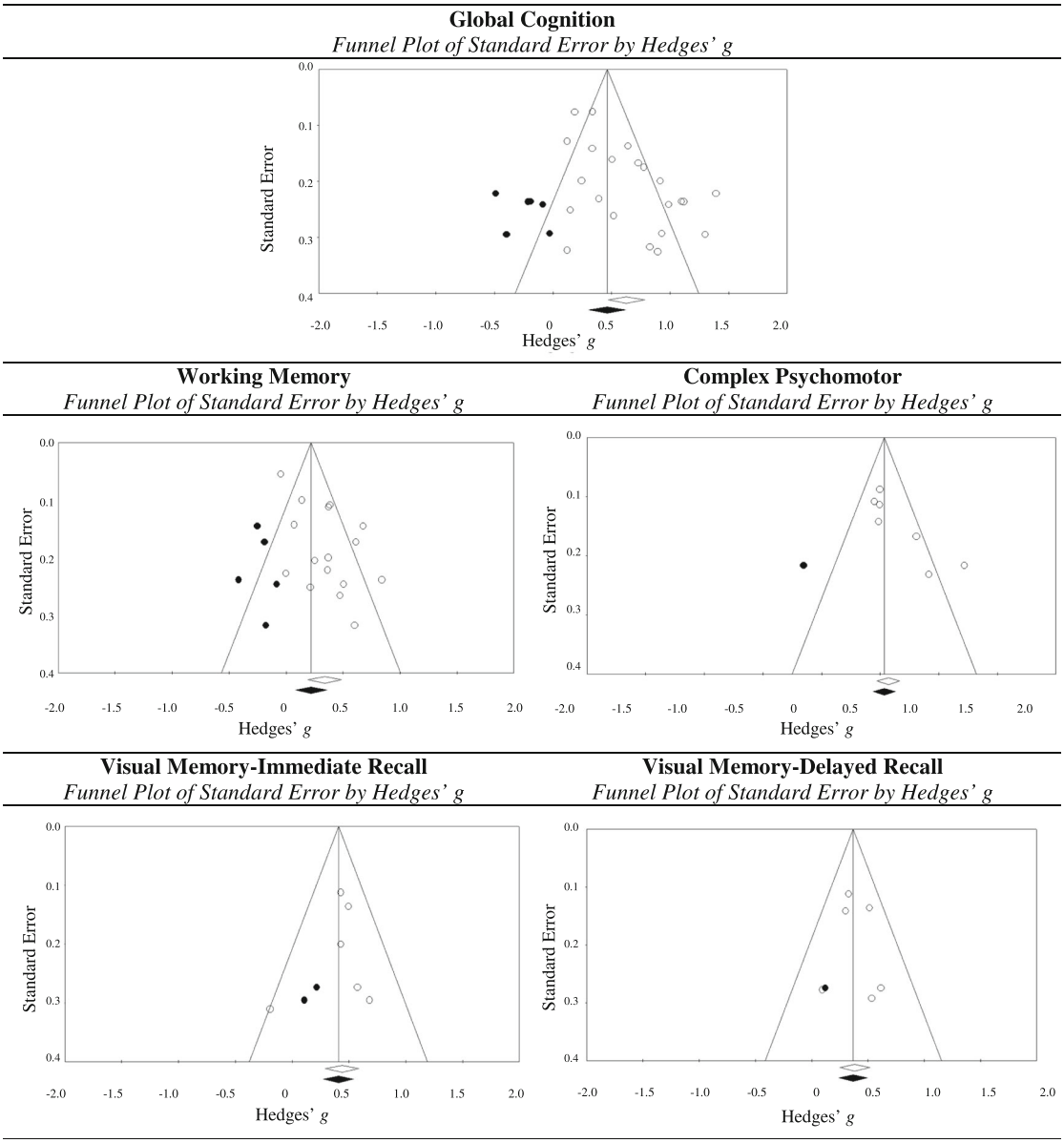

Fig. 2 Funnel plots of the domains with possible overestimates of effect sizes. The filled circles are the potential missing studies, whereas the open circles are the observed studies in the analysis. Similarly, the filled triangles are the adjusted effect sizes, while the open triangles are the observed effect sizes

therefore, additional research is essential to determine the sensitivity and specificity of these brief tests.

Complex psychomotor speed, processing speed, and verbal fluency domains evidenced statistically significant medium effect sizes. Complex psychomotor speed was mostly assessed by Digit Symbol Substitution Test (DSST) and Symbol Digit Modalities Test (SDMT). It has been theorized that the SDMT may require a higher degree of fine motor coordination and working memory because this task requires an individual to draw novel symbols rather than well-rehearsed numbers. In contrast, the DSST is less dependent on these abilities. Therefore, it was unsurprising that the effect size associated with the SDMT ($g = 1.079$) was almost double the one associated with DSST ($g = 0.512$). Processing speed had a statistically significant medium effect and was most commonly measured by the Trail Making Test-Part A. The verbal fluency domain was comprised of phonemic (i.e., FAS) and semantic fluency (i.e., Animal naming). Given that these two language-mediated tests yielded similar effect sizes, the results support the involvement of both frontal and medial temporal lobes in heart failure (Lezak et al., 2012).

In contrast to the previous domains that exhibited medium effect sizes, working memory ($g = 0.339$), and simple attention ($g = 0.278$) yielded small but statistically significant effect sizes. Attention was most frequently measured by Digit Span-Forward, while working memory was regularly

measured by Digit Span-Backward. Given these small effect sizes, if these neuropsychological abilities were found to be significantly impaired in an individual with heart failure, it is possible that other functions might also be impeded.

Limitations and Future Directions

Given the multidimensional nature of neuropsychological performance-based tests, meta-analyses that attempt to examine domains of functioning using these tools are limited by having to categorize them in a unidimensional fashion. This is due to the need for maintaining independence of observations while maximizing the data that can be included in the meta-analysis. In order to reduce the impact of this limitation, individual tests and measures in this study were assigned to domains and composites based on previously published articles (Hall et al., 2018; Wollman et al., 2019), data provided by test manuals and compendiums (Strauss et al., 2006), and evidenced-based clinical interpretation found in major references about neuropsychological assessment (Lezak et al., 2012).

Another limitation of this current meta-analysis is the number of small studies across domains which prevented moderation analyses (Borenstein, 2011). Given the heterogeneity found in multiple domains and tests, it would have been useful to examine variables such as ejection fraction, heart failure severity, etiology, and heart failure type to determine if they had a role in the observed variance. In order to ameliorate this shortcoming, sensitivity analyses were performed to determine if single articles were responsible for considerable amounts of heterogeneity ($I^2 > 75\%$). Three articles were shown to have a significant impact on the level of heterogeneity and had large effect sizes. These articles also included the most severe heart failure group based on NYHA classification and/or ejection fraction less than 20. Specifically, Nordlund et al. (2105) had the largest effect size while having the highest degree of severity in the heart failure group compared to the other two studies. Similarly, the article by Moryś et al. (2016) contributed significantly to the heterogeneity observed at the domain- and test-level.

Given that the observed effect sizes in this current study were small to medium, one practical implication is that the impact of heart failure on cognition is potentially small enough to improve with heart failure treatment. Therefore, research is warranted to determine the long-term efficacy of cardiac interventions such as left ventricular assist devices and heart transplants toward improving cognition. An example of such research was done by Petrucci et al. (2012), who continually assessed neuropsychological performance among patients who received an left ventricular assist device over six months. The results from the study supported continuous improvements in visual memory and executive function at a 1-month, 3-month, and 6-month follow-up (Petrucci et al., 2012). Other research supports the potential reversibility of cognitive impairments following a heart transplant. For example, patients who demonstrate improvement in cardiac functioning, such as increased ejection fraction and an improved cardiac index, also demonstrate increased cognitive functioning (Hajduk, Kiefe, Person, Gore, & Saczynski, 2013). When enough studies have been done, meta-analyses could be useful in determining the robustness of the effects of such interventions on cognition.

Another area for future research is to determine the role of cardiac biomarkers in predicting neurocognitive status in heart failure. The use of cardiac biomarkers has been shown to predict cognitive performance in individuals with heart failure (Festa et al., 2011; Jesus et al., 2006; Pressler et al., 2010). In one study, impaired ejection fraction was associated with impaired verbal memory performance in older adults; however, this relationship was not observed in younger adults with heart failure (Festa et al., 2011). Impaired blood flow in the middle cerebral artery (MCA) has also been shown to be predictive of scores on the MMSE in this clinical population (Jesus et al., 2005). Low ejection fraction, along with lower scores on tests of global cognitive function, working memory, verbal memory, psychomotor speed, and executive function, were significant predictors of mortality at a one-year follow-up (Pressler et al., 2010). Although these primary studies support the relationship between heart failure biomarkers, neuropsychological function, and outcomes, these variables were not reported consistently in the literature to facilitate sufficiently powered moderation analyses in the current study.

Conclusions

Overall, the results of this meta-analysis support that the general heart failure population (NYHA Class II and III) perform mildly worse than a comparison group across most neuropsychological domains. The effect sizes observed in this study ranged from small to medium, with the greatest impact on higher-level neurocognitive processes. These small-to-medium effect sizes suggest that the general heart failure population may not have overt cognitive impairments at an individual level; however, completing tasks in everyday life may be more effortful. Some deviations from the norm are likely to be observed when evaluating the cognitive functioning of individuals with NYHA Class IV using screening instruments as well as more comprehensive neuropsychological testing. It is important to screen and track neurocognition in this clinical population as there appears to be diffuse cerebral involvement in heart failure, as well as opportunities to

inform future medical treatment and improve patient care management.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s11065-020-09463-3.

References

Adebayo, P. B., Akintunde, A. A., Audu, M. B., Ayodele, O. E., Akinyemi, R. O., & Opadijo, O. G. (2016). Profile and determinants of neurocognitive dysfunction in a sample of adult Nigerians with heart failure. *Journal of Cardiovascular Nursing*, *31*(6), 535–544. https://doi.org/10.1097/jcn.0000000000000289

Agarwal, K. S., Kazim, R., Xu, J., Borson, S., & Taffet, G. E. (2016). Unrecognized cognitive impairment and its effect on heart failure readmissions of elderly adults. *Journal of American Geriatric Society*, *64*(11), 2296–2301. https://doi.org/10.1111/jgs.14471

Alagiakrishnan, K., Mah, D., Dyck, J. R., Senthilselvan, A., & Ezekowitz, J. (2017). Comparison of two commonly used clinical cognitive screening tests to diagnose mild cognitive impairment in heart failure with the golden standard European consortium criteria. *International Journal of Cardiology*, *228*, 558–562. https://doi.org/10.1016/j.ijcard.2016.11.193

Aldrugh, S., Sardana, M., Henninger, N., Saczynski, J. S., & McManus, D. D. (2017). Atrial fibrillation, cognition and dementia: A review. *Journal of Cardiovascular Electrophysiology*, *28*(8), 958–965. https://doi.org/10.1111/jce.13261

Almeida, O. P., Beer, C., Lautenschlager, N. T., Arnolda, L., Alfonso, H., & Flicker, L. (2012). Two-year course of cognitive function and mood in adults with congestive heart failure and coronary artery disease: The heart-mind study. *International Psychogeriatrics*, *24*(1), 38–47. https://doi.org/10.1017/s1041610211001657

Almeida, O. P., & Tamai, S. (2001). Congestive heart failure and cognitive functioning amongst older adults. *Arquivos de Neuro-Psiquiatria*, *59*(2B), 324–329.

Alosco, M. L., Gunstad, J., Jerskey, B. A., Clark, U. S., Hassenstab, J. J., Xu, X., & Sweet, L. H. (2013). Left atrial size is independently associated with cognitive function. *International Journal of Neuroscience*, *123*(8), 544–552. https://doi.org/10.3109/00207454.2013.774396

Alosco, M. L., Spitznagel, M. B., Cohen, R., Raz, N., Sweet, L. H., Josephson, R., & Gunstad, J. (2014). Reduced cerebral perfusion predicts greater depressive symptoms and cognitive dysfunction at a 1-year follow-up in patients with heart failure. *International Journal of Geriatric Psychiatry*, *29*(4), 428–436. https://doi.org/10.1002/gps.4023

Alosco, M. L., Spitznagel, M. B., Sweet, L. H., Josephson, R., Hughes, J., & Gunstad, J. (2015). Atrial fibrillation exacerbates cognitive dysfunction and cerebral perfusion in heart failure. *Pacing and Clinical Electrophysiology*, *38*(2), 178–186. https://doi.org/10.1111/pace.12543

Alves, T. C., Rays, J., Telles, R. M., Junior, R. F., Wajngarten, M., Romano, B. W., & Busatto, G. F. (2007). Effects of antidepressant treatment on cognitive performance in elderly subjects with heart failure and comorbid major depression: An exploratory study. *Psychosomatics*, *48*(1), 22–30. https://doi.org/10.1176/appi.psy.48.1.22

Alwerdt, J., Edwards, J. D., Athilingam, P., O'Connor, M. L., & Valdes, E. G. (2013). Longitudinal differences in cognitive functioning among older adults with and without heart failure. *Journal of Aging and Health*, *25*(8), 1358–1377. https://doi.org/10.1177/0898264313505111

Athilingam, P., D'Aoust, R. F., Miller, L., & Chen, L. (2013). Cognitive profile in persons with systolic and diastolic heart failure. *Congestive Heart Failure*, *19*(1), 44–50. https://doi.org/10.1111/chf.12001

Beer, C., Ebenezer, E., Fenner, S., Lautenschlager, N. T., Arnolda, L., Flicker, L., & Almeida, O. P. (2009). Contributors to cognitive impairment in congestive heart failure: A pilot case-control study. *International Medical Journal*, *39*(9), 600–605. https://doi.org/10.1111/j.1445-5994.2008.01790.x

Bhat, G., Yost, G., & Mahoney, E. (2015). Cognitive function and left ventricular assist device implantation. *The Journal of Heart and Lung Transplantation*, *24*(11), 1398–1405. https://doi.org/10.1016/j.healun.2015.05.015

Borenstein, M., Hedges, L. V., Higgins, J. P., & Rothstein, H. R. (2011). Introduction to meta-analysis. John Wiley & Son.

Borenstein, M., Higgins, J. P., Hedges, L. V., & Rothstein, H. R. (2017). Basics of meta-analysis: I2 is not an absolute measure of heterogeneity. *Research Synthesis Methods*, *8*(1), 5–18.

Caruso, P., Signori, R., & Moretti, R. (2019). Small vessel disease to subcortical dementia: A dynamic model, which interfaces aging, cholinergic dysregulation and the neurovascular unit. *Vascular Health and Risk Management*, *15*, 259–281. https://doi.org/10.2147/VHRM.S190470

Chou, C. C., Pressler, S. J., & Giordani, B. (2014). Predictors of memory performance among Taiwanese postmenopausal women with heart failure. *Journal of Cardiac Failure*, *20*(9), 679–688. https://doi.org/10.1016/j.cardfail.2014.06.002

Cohen, J. (1992). A power primer. *Psychological Bulletin, 112*(1), 155–159. https://doi.org/10.1037//0033-2909.112.1.155

de la Torre, J. C. (2012). Cardiovascular risk factors promote brain hypoperfusion leading to cognitive decline and dementia. *Cardiovascular Psychiatry and Neurology*, *2012*, 1–15.

Festa, J. R., Jia, X., Cheung, K., Marchidann, A., Schmidt, M., Shapiro, P. A., & Lazar, R. M. (2011). Association of low ejection fraction with impaired verbal memory in older patients with heart failure. *Archives of Neurology*, *68*(8), 1021–1026. https://doi.org/10.1001/archneurol.2011.163

Frey, A., Sell, R., Homola, G. A., Malsch, C., Kraft, P., Gunreben, I., & Stoll, G. (2018). Cognitive deficits and related brain lesions in patients with chronic heart failure. *Journal of American College of Cardiology: Heart Failure*, *6*(7), 583–592. https://doi.org/10.1016/j.jchf.2018.03.010

Gates, N. J., & March, E. G. (2016). A neuropsychologist's guide to undertaking a systematic review for publication: Making the most of PRISMA guidelines. *Neuropsychology Review*, *26*(2), 109–120.

Goodall, J., Fisher, C., Hetrick, S., Phillips, L., Parrish, E. M., & Allott, K. (2018). Neurocognitive functioning in depressed young people: A systematic review and meta-analysis. *Neuropsychology Review*, *28*(2), 216–231. https://doi.org/10.1007/s11065-018-9373-9

Grimm, G. (1996). Congestive heart failure/ventricular hypertrophy/heart transplantation may affect improvement of cognitive brain function after successful cardiac transplantation.

Grubb, N. R., Simpson, C., & Fox, K. A. (2000). Memory function in patients with stable, moderate to severe cardiac failure. *American Heart Journal*, *140*(1), E1–E5.

Habota, T., McLennan, S. N., Cameron, J., Henry, J. D., Ski, C. F., Thompson, D. R., & Rendell, P. G. (2015). Prospective memory impairment in chronic heart failure. *Journal of the International Neuropsychological Society*, *21*(3), 183–192. https://doi.org/10.1017/s1355617715000119

Hajduk, A. M., Kiefe, C. I., Person, S. D., Gore, J. G., & Saczynski, J. S. (2013). Cognitive change in heart failure: A systematic review. *Circulation. Cardiovascular Quality and Outcomes*, *6*(4), 1–20. https://doi.org/10.1161/circoutcomes.113.000121

Hall, M. G., Hauson, A. O., Wollman, S. C., Allen, K. E., Connors, E. J., Stern, M. J., & Grant, I. (2018). Neuropsychological comparisons of

cocaine versus methamphetamine users: A research synthesis and meta-analysis. *The American Journal of Drug and Alcohol Abuse*, *44*(3), 277–293. https://doi.org/10.1080/00952990.2017.1355919

Hammond, C. A., Blades, N. J., Chaudhry, S. I., Dodson, J. A., Longstreth Jr., W. T., Heckbert, S. R., … Gardin, J. M. (2018). Long-term cognitive decline after newly diagnosed heart failure: Longitudinal analysis in the CHS (Cardiovascular Health Study). *Circulation: Heart Failure*, *11*(3), e004476. https://doi.org/10.1161/circheartfailure.117.004476

Harkness, K., Heckman, G. A., Akhtar-Danesh, N., Demers, C., Gunn, E., & McKelvie, R. S. (2014). Cognitive function and self-care management in older patients with heart failure. *European Journal of Cardiovascular Nursing*, *13*(3), 277–284. https://doi.org/10.1177/1474515113492603

Higgins, J. P., & Green, S. (Eds.). (2011). *Cochrane handbook for systematic reviews of interventions* (Vol. 4). John Wiley & Sons.

Hjelm, C., Dahl, A., Brostrom, A., Martensson, J., Johansson, B., & Stromberg, A. (2012). The influence of heart failure on longitudinal changes in cognition among individuals 80 years of age and older. *Journal of Clinical Nursing*, *21*(7–8), 994–1003. https://doi.org/10.1111/j.1365-2702.2011.03817.x

Hoth, K. F., Poppas, A., Moser, D. J., Paul, R. H., & Cohen, R. A. (2008). Cardiac dysfunction and cognition in older adults with heart failure. *Cognitive and Behavioral Neurology*, *21*(2), 65–72. https://doi.org/10.1097/WNN.0b013e3181799dc8

Jesus, P. A., Vieira-de-Melo, R. M., Reis, F. J., Viana, L. C., Lacerda, A., Dias, J. S., & Oliveira-Filho, J. (2006). Cognitive dysfunction in congestive heart failure: Transcranial Doppler evidence of microembolic etiology. *Arq Neuropsiquiatr*, *64*(2a), 207–210.

Jung, M., Jonides, J., Northouse, L., Berman, M. G., Koelling, T. M., & Pressler, S. J. (2016). Randomized crossover study of the natural restorative environment intervention to improve attention and mood in heart failure. *Journal of Cardiovascular Nursing*, *32*(5), 464–479. https://doi.org/10.1097/jcn.0000000000000368

Kemp, C. D., & Conte, J. V. (2012). The pathophysiology of heart failure. *Cardiovascular Pathology*, *2*(5), 365–271. https://doi.org/10.1016/j.carpath.2011.11.007

Kim, J., Shin, M. S., Hwang, S. Y., Park, E., Lim, Y. H., Shim, J. L., & An, M. (2018). Memory loss and decreased executive function are associated with limited functional capacity in patients with heart failure compared to patients with other medical conditions. *Heart & Lung*, *47*(1), 61–67. https://doi.org/10.1016/j.hrtlng.2017.09.005

Kindermann, I., Fischer, D., Karbach, J., Link, A., Walenta, K., Barth, C., & Böhm, M. (2012). Cognitive function in patients with decompensated heart failure: The cognitive impairment in heart failure (CogImpair-HF) study. *European Journal of Heart Failure*, *14*(4), 404–413. https://doi.org/10.1093/eurjhf/hfs015

Komori, T., Eguchi, K., Saito, T., Nishimura, Y., Hoshide, S., & Kario, K. (2016). Riser blood pressure pattern is associated with mild cognitive impairment in heart failure patients. *American Journal of Hypertension, 29*(2), 194–201. https://doi.org/10.1093/ajh/hpv086

Kumar, R., Yadav, S. K., Palomares, J. A., Park, B., Joshi, S. H., Ogren, J. A., & Woo, M. A. (2015). Reduced regional brain cortical thickness in patients with heart failure. *PLoS One*, *10*(5), e0126595. https://doi.org/10.1371/journal.pone.0126595

Kure, C. E., Rosenfeldt, F. L., Scholey, A. B., Pipingas, A., Kaye, D. M., Bergin, P. J., & Stough, C. (2016). Relationships among cognitive function and cerebral blood flow, oxidative stress, and inflammation in older heart failure patients. *Journal of Cardiac Failure*, *22*(7), 548–559. https://doi.org/10.1016/j.cardfail.2016.03.006

Lavery, L., Bilt, J. V., Chang, C.-C. H., Saxton, J. A., & Ganguli, M. (2007). The association between congestive heart failure and cognitive performance in a primary care population of elderly adults: The Steel Valley Seniors Survey. *International Psychogeriatrics*, *19*(2), 215–225. https://doi.org/10.1017/S1041610206003449

Lezak, M. D., Howieson, D. B., Bigler, E. D., & Tranel, D. (2012). *Neuropsychological assessment* (5th ed.). New York, NY, US: Oxford University Press.

Mapelli, D., Cavazzana, A., Cavalli, C., Bottio, T., Tarzia, V., Gerosa, G., & Volpe, B. R. (2014). Clinical psychological and neuropsychological issues with left ventricular assist devices (LVADs). *Annals of Cardiothoracic Surgery*, *3*(5), 480–489.

Meguro, T., Meguro, Y., & Kunieda, T. (2017). Atrophy of the parahippocampal gyrus is prominent in heart failure patients without dementia. *ESC Heart Fail*, *4*(4), 632–640. https://doi.org/10.1002/ehf2.12192

Moher, D., Shamseer, L., Clarke, M., Ghersi, D., Liberati, A., Petticrew, M., & Stewart, L. A. (2015). Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews*, *4*(1), 1. https://doi.org/10.1186/2046-4053-4-1

Moon, C., Yoon, J. Y., & Bratzke, L. C. (2016). The role of heart failure, daytime sleepiness, and disturbed sleep on cognition. *Western Journal of Nursing Research*, *9*(4), 473–491. https://doi.org/10.1177/0193945916675587

Moryś, J. M., Pąchalska, M., Bellwon, J., & Gruchała, M. (2016). Cognitive impairment, symptoms of depression, and health-related quality of life in patients with severe stable heart failure. *International Journal of Clinical and Health Psychology*, *16*(3), 230–238. https://doi.org/10.1016/j.ijchp.2016.03.002

Mozaffarian, D., Benjamin, E. J., Go, A. S., Arnett, D. K., Blaha, M. J., Cushman, M., & Turner, M. B. (2016). Heart disease and stroke statistics-2016 update: A report from the American Heart Association. *Circulation*, *133*, e38–e360. https://doi.org/10.1161/CIR.0000000000000350

National Heart, Lung, and Blood Institute. (2014). *Quality assessment tool for observational cohort and cross-sectional studies*. Bethesda: National Institutes of Health, Department of Health and Human Services.

Niizeki, T., Iwayama, T., Ikeno, E., & Watanabe, M. (2019). Prognostic importance of hippocampal atrophy in patients with chronic heart failure. *The American Journal of Cardiology, 123*(7), 1109–1113. https://doi.org/10.1016/j.amjcard.2018.12.035

Nikendei, C., Schäfer, H., Weisbrod, M., Huber, J., Geis, N., Katus, H. A., & Schultz, J.-H. (2016). The effects of mitral valve repair on memory performance, executive function, and psychological measures in patients with heart failure. *Psychosomatic Medicine*, *78*(4), 432–442. https://doi.org/10.1097/PSY.0000000000000284

Nordlund, A., Berggren, J., Holmstrom, A., Fu, M., & Wallin, A. (2015). Frequent mild cognitive deficits in several functional domains in elderly patients with heart failure without known cognitive disorders. *Journal of Cardiac Failure*, *21*(9), 702–707. https://doi.org/10.1016/j.cardfail.2015.04.006

Parsons, M. W., Hammeke, T. A., & Snyder, P. J. (2014). *Clinical neuropsychology: A pocket handbook for assessment*. American Psychological Association.

Petrucci, R. J., Rogers, J. G., Blue, L., Gallagher, C., Russell, S. D., Dordunoo, D., & Slaughter, M. S. (2012). Neurocognitive function in destination therapy patients receiving continuous-flow vs pulsatile-flow left ventricular assist device support. *The Journal of Heart and Lung Transplantation*, *31*(1), 27–36. https://doi.org/10.1016/healun.2011.10.012

Prado, C. E., Watt, S., & Crowe, S. F. (2018). A meta-analysis of the effects of antidepressants on cognitive functioning in depressed and non-depressed samples. *Neuropsychology Review*, *28*(1), 32–72. https://doi.org/10.1007/s11065-018-9369-5

Pressler, S. J., Subramanian, U., Kareken, D., Perkins, S. M., Gradus-Pizlo, I., Sauve, M. J., & Shaw, R. M. (2010). Cognitive deficits in chronic heart failure. *Nursing Research*, *59*(2), 127–139. https://doi.org/10.1097/NNR.0b013e3181d1a747

Putzke, J. D., Williams, M. A., Daniel, F. J., Bourge, R. C., & Boll, T. J. (2000). Activities of daily living among heart transplant candidates:

Neuropsychological and cardiac function predictors. *Journal of Heart and Lung Transportation*, *19*(10), 995–1006.

Qiu, C., Winblad, B., Marengoni, A., Klarin, I., Fastbom, J., & Fratiglioni, L. (2006). Heart failure and risk of dementia and Alzheimer disease. *Archives of Internal Medicine*, *166*(9), 1003. https://doi.org/10.1001/archinte.166.9.1003

Roy, B., Woo, M. A., Wang, D. J. J., Fonarow, G. C., Harper, R. M., & Kumar, R. (2017). Reduced regional cerebral blood flow in patients with heart failure. *European Journal of Heart Failure*, *19*(10), 1294–1302. https://doi.org/10.1002/ejhf.874

Schmidt, R., Fazekas, F., Offenbacher, H., Dusleag, J., & Lechner, H. (1991). Brain magnetic resonance imaging and neuropsychologic evaluation of patients with idiopathic dilated cardiomyopathy. *Stroke*, *22*(2), 195–199.

Siachos, T., Vanbakel, A., Feldman, D. S., Uber, W., Simpson, K. N., & Pereira, N. L. (2005). Silent strokes in patients with heart failure. *Journal of Cardiac Failure, 11*(7), 485–489. https://doi.org/10.1016/j.cardfail.2005.04.004

Stanek, K. M., Gunstad, J., Paul, R. H., Poppas, A., Jefferson, A. L., Sweet, L. H., & Cohen, R. A. (2009). Longitudinal cognitive performance in older adults with cardiovascular disease: Evidence for improvement in heart failure. *Journal of Cardiovascular Nursing*, *24*(3), 192–197. https://doi.org/10.1097/JCN.0b013e31819b54de

Staniforth, A. D., Kinnear, W. J., & Cowley, A. J. (2001). Cognitive impairment in heart failure with Cheyne-stokes respiration. *Heart*, *85*(1), 18–22.

Stephan, R. A., Alhassoon, O. M., Allen, K. E., Wollman, S. C., Hall, M., Thomas, W. J., & Dalenberg, C. J. (2017). Meta-analyses of clinical neuropsychological tests of executive dysfunction and impulsivity in alcohol use disorder. *The American Journal of Drug and Alcohol Abuse*, *43*(1), 24–43. https://doi.org/10.1080/00952990.2016.1206113

Strauss, E., Sherman, E. M. S., & Spreen, O. (2006). *A compendium of neuropsychological tests: Administration, norms, and commentary* (3rd ed.). New York: Oxford University Press.

Suavé, M. J., Lewis, W. R., Blankenbiller, M., Rickabaugh, B., & Pressler, S. J. (2009). Cognitive impairments in chronic heart failure: A case-controlled study. *Journal of Cardiac Failure*, *15*(1), 1–10. https://doi.org/10.1016/j.cardfail.2008.09.007

Suchy, Y. (2015). *Executive functioning: A comprehensive guide for clinical practice*. Oxford University Press.

Trojano, L., Antonelli Incalzi, R., Acanfora, D., Picone, C., Mecocci, P., & Rengo, F. (2003). Cognitive impairment: A key feature of congestive heart failure in the elderly. *Journal of Neurology*, *250*(12), 1456–1463. https://doi.org/10.1007/s00415-003-0249-3

Viechtbauer, W., & Cheung, M. W. L. (2010). Outlier and influence diagnostics for meta-analysis. *Research Synthesis Methods*, *1*(2), 112–125. https://doi.org/10.1002/jrsm.11

Vogels, R. L., Oosterman, J. M., van Harten, B., Scheltens, P., van der Flier, W. M., Schroeder-Tanka, J. M., & Weinstein, H. C. (2007). Profile of cognitive impairment in chronic heart failure. *Journal of American Geriatrics Society*, *55*(11), 1764–1770. https://doi.org/10.1111/j.1532-5415.2007.01395.x

Weintraub, S., Wicklund, A. H., & Salmon, D. P. (2012). The neuropsychological profile of Alzheimer disease. *Cold Spring Harbor Perspectives in Medicine*, *2*(4), a006171. https://doi.org/10.1101/cshperspect.a006171

Wollman, S. C., Hauson, A. O., Hall, M. G., Connors, E. J., Allen, K. E., Stern, M. J., & Flora-Tostado, C. (2019). Neuropsychological functioning in opioid use disorder: A research synthesis and meta-analysis. *The American Journal of Drug and Alcohol Abuse*, *45*(1), 11–25. https://doi.org/10.1080/00952990.2018.1517262

Woo, M. A., Yadav, S. K., Macey, P. M., Fonarow, G. C., Harper, R. M., & Kumar, R. (2014). Brain metabolites in autonomic regulatory insular sites in heart failure. *Journal of the Neurological Sciences, 346*(1–2), 271–275. https://doi.org/10.1016/j.jns.2014.09.006

Woo, M. A., Ogren, J. A., Abouzeid, C. M., Macey, P. M., Sairafian, K. G., Saharan, P. S., & Kumar, R. (2015a). Regional hippocampal damage in heart failure. *European Journal of Heart Failure*, *17*(5), 494–500. https://doi.org/10.1002/ejhf.241

Woo, M. A., Palomares, J. A., Macey, P. M., Fonarow, G. C., Harper, R. M., & Kumar, R. (2015b). Global and regional brain mean diffusivity changes in patients with heart failure. *Journal of Neuroscience Research*, *93*(4), 678–685. https://doi.org/10.1002/jnr.23525

Yohannes, A. M., Chen, W., Moga, A. M., Leroir, I., & Connolly, M. J. (2017). Cognitive impairment in chronic obstructive pulmonary disease and chronic heart failure: A systematic review and meta-analysis of observational studies. *Journal of the American Medical Directors Association*, *11*(5), S1525–S8610. https://doi.org/10.1016/j.jamda.2017.01.014