Published in final edited form as:

J Card Fail. 2009 April ; 15(3): 214–223. doi:10.1016/j.cardfail.2008.10.020.

Brain Injury in Autonomic, Emotional, and Cognitive Regulatory Areas in Patients with Heart Failure

Mary A. Woo, DNSc, RN^{1,*}, Rajesh Kumar, PhD³, Paul M. Macey, PhD^{1,2}, Gregg C. Fonarow, MD⁴, and Ronald M. Harper, PhD^{2,3}

¹School of Nursing; University of California at Los Angeles, Los Angeles, CA 90095, USA

²Brain Research Institute; University of California at Los Angeles, Los Angeles, CA 90095, USA

³Department of Neurobiology, University of California at Los Angeles, Los Angeles, CA 90095, USA

⁴Department of Cardiology, David Geffen School of Medicine, University of California at Los Angeles, Los Angeles, CA 90095, USA

Abstract

Background—Heart failure (HF) is accompanied by autonomic, emotional, and cognitive deficits, indicating brain alterations. Reduced gray matter volume and isolated white matter infarcts occur in HF, but the extent of damage is unclear. Using magnetic resonance T2 relaxometry, we evaluated the extent of injury across the entire brain in HF.

Methods and Results—Proton-density and T2-weighted images were acquired from 13 HF (age 54.6 ± 8.3 years; 69% male, LVEF 0.28 ± 0.07) and 49 controls (50.6 ± 7.3 years, 59% male). Whole brain maps of T2 relaxation times were compared at each voxel between groups using analysis of covariance (covariates: age and gender). Higher T2 relaxation values, indicating injured brain areas ($p < 0.005$), emerged in sites that control autonomic, analgesic, emotional, and cognitive functions (hypothalamus, raphé magnus, cerebellar cortex, deep nuclei and vermis; temporal, parietal, prefrontal, occipital, insular, cingulate, and ventral frontal cortices; corpus callosum; anterior thalamus; caudate nuclei; anterior fornix and hippocampus). No brain areas showed higher T2 values in control vs. HF subjects.

Conclusions—Brain structural injury emerged in areas involved in autonomic, pain, mood, language, and cognitive function in HF patients. Comorbid conditions accompanying HF may result from neural injury associated with the syndrome.

Keywords

Depression; T2-relaxometry; Dyspnea; Pain

Address for Correspondence: Mary A. Woo, DNSc, RN, Professor – UCLA School of Nursing, 700 Tiverton Avenue, Los Angeles, CA 90095-1702, Tel: (310) 206-2032, FAX: (310) 206-7433, Email: mwoo@sonnet.ucla.edu.

Conflict of interest: Authors declare no conflicts of interest.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Introduction

The incidence of heart failure (HF) in the United States has increased by 14% in the last decade, and nearly half of patients discharged for HF require re-hospitalization within six months (1-2). The increased incidence of HF and re-hospitalization rates demand strategies to improve survival, morbidity, and quality of life. Several of these strategies, such as gaining control over autonomic nervous system (ANS) dysfunction, modulating pain, and enhancing self-care (which requires relatively unimpaired cognitive abilities of the patient), depend on adequate central nervous system (CNS) function. However, there is increasing evidence of physiological and neuropsychological aberrations resulting from disturbed integrity of the CNS in HF, with ANS dysfunction (3), altered pain thresholds (4,5), and emotional and cognitive abnormalities (depression, short-term memory loss) (6,7) being especially apparent. Brain structural injury, including scattered cerebral infarcts (8) and specific sites of gray matter volume loss (9), occur in the syndrome, and may contribute to the physiological and behavioral deficits in HF (10).

Despite evidence of CNS abnormalities in HF, and the potential influence that such damage to brain structures could exert on autonomic, emotional, and cognitive behaviors, only limited reports of structural brain injury in HF exist. Available studies demonstrate hyperintensities in white matter (11) and volume loss in specific gray matter regions (9) based on magnetic resonance imaging (MRI), but do not address the extent or type of damage throughout the entire brain, especially of fiber systems which interconnect different brain structures.

Magnetic resonance T2 relaxometry measures free-water content in tissue; values increase with tissue injury, and can assess both gray (12) and white matter (13) integrity over the entire brain. The specific aim of this study was to determine regional brain injury in HF patients which may underlie the ANS, cognitive, and emotional deficits using T2 relaxometry procedures.

Methods

Subjects

Thirteen hemodynamically optimized HF patients (age range 40 - 64 years; mean age $\pm$ SD = 54.6 ± 8.3 years; 9 male) and 49 control subjects (39 - 64 years; mean 50.6 ± 7.3 years; 29 male) were studied. All HF patients were diagnosed based on national HF diagnostic criteria (14), showed systolic dysfunction and dilated cardiomyopathy, and were classified as New York Heart Association Functional Class II (and thus were able to lay flat in the MRI scanner). Mean left ventricular ejection fraction for HF subjects was 0.28 ± 0.07 . Four (31%) of the HF subjects had type II diabetes. All HF patients were treated with angiotension-converting enzyme inhibitors or angiotensin receptor blockers, beta blockers, and diuretics to maintain stable body weight for at least six months before collection of study data. The HF subjects were recruited from the Ahmanson-University of California at Los Angeles Cardiomyopathy Center and the Los Angeles community via study flyers.

All control subjects were without history of cardiovascular, cerebrovascular, respiratory, or neurological disorder (i.e., no history of hypertension, hyperlipidemia, diabetes, depression, obstructive pulmonary disease, stroke), with no cardiac or psychotropic medications, and recruited through advertisements at the university campus. Exclusion criteria for HF and control subjects were claustrophobia, loose/non-removable metal (such as braces, embolic coils, pacemakers/implantable cardioverter-defibrillators, stents), and inability to lay supine.

Control and HF subjects provided written consent before the study, and the protocol was approved by the Institutional Review Board of the University of California at Los Angeles.

Magnetic Resonance Imaging

Images of the entire brain were collected using a 3.0 Tesla MRI scanner (Siemens, Magnetom Tim-Trio, Erlangen, Germany) while subjects lay supine. Head motion during scanning was minimized by placing foam pads on either side of the head. Proton-density and T2-weighted images [repetition time = 10,000 ms; echo-times = 17, 134 ms; flip angle = 130°; turbo factor = 5; matrix size = 256 × 256; field of view = 230 × 230 mm; slice thickness = 4.0 mm; scan time = 5:02 min] were collected simultaneously using a dual-echo turbo spin-echo pulse sequence in the axial plane. High-resolution T1-weighted images for evaluation of anatomical defects and structural identification were also collected using a magnetization prepared rapid acquisition gradient-echo pulse sequence (repetition time = 2200 ms; echo-time = 2.2 ms; inversion time = 900 ms; flip angle = 9°; matrix size = 256 × 256; field of view = 230 × 230 mm; slice thickness = 1.0 mm; scan time = 5:25 min).

Data evaluation and processing

T1-weighted, proton-density-weighted, and T2-weighted brain images were visually assessed for any serious anatomical defects such as cystic lesions, major infarcts, or other mass lesions. Proton-density and T2-weighted images were also evaluated for motion artifacts. Two HF and four control subjects showed motion artifacts and were excluded, leaving the previously-described 13 HF and 49 control subjects for analysis.

We used the statistical parametric mapping package SPM5 (Wellcome Department of Cognitive Neurology, UK; <http://www.fil.ion.ucl.ac.uk/spm/>), and Matlab-based (The MathWorks Inc, Natick, MA) custom software for data processing.

Voxel-by-voxel T2 relaxation values were calculated using proton-density and T2-weighted images as described earlier (15,16). Whole-brain T2 maps were constructed using T2 relaxation values calculated for each voxel and normalized to a common space. For normalization of T2 maps, T2-weighted images of each subject were normalized to the Montreal Neurological Institute space, using *a priori* defined distributions of tissue types, and the resulting parameters were applied to the corresponding T2 maps. The normalized T2 maps were smoothed (Gaussian filter, full-width-at-half-maximum = 10 mm).

Data Analysis

Demographic data—The demographic data were analyzed with the Statistical Package for the Social Sciences (SPSS, v 15.0, Chicago, IL). The numerical demographic data and characteristics of HF and control subjects were compared with unpaired *t*-tests and categorical characteristics were compared using Chi-square tests. A statistical threshold of $p < 0.05$ was considered significant.

Voxel-based-relaxometry—We used voxel-based-relaxometry, a voxel-based analysis of T2 relaxation times, for brain MRI data analysis (17). Voxel-based-relaxometry allows comparison of T2 relaxation values across the whole brain and shows regional differences between groups. The normalized and smoothed T2 maps of HF and control subjects were compared at each voxel using analysis of covariance, with age and gender included as covariates. Statistical parametric maps of significantly increased T2 values were displayed ($p < 0.005$, uncorrected) and clusters with T2 value differences between groups were overlaid onto a spatially normalized T1-weighted image, the Montreal Neurological Institute reference brain.

Region-of-interest analyses—We also performed region-of-interest (ROI) analyses to assess the magnitude of T2 relaxation value differences between groups for brain sites that showed injury on voxel-based-relaxometry. Regions-of-interest masks of different brain areas,

using clusters determined abnormal by voxel-based-relaxometry procedures, were extracted and used to calculate T2 relaxation values from normalized and smoothed individual's T2 relaxation maps. T2 relaxation values of different brain sites were compared between HF and control groups using multivariate analysis of covariance, with age and gender included as covariates.

Results

Demographic data

Demographic data of the HF and control subjects are summarized in Table 1. HF subjects had higher body mass index values, and two had non-sinus rhythm.

Voxel-based-relaxometry

Abnormal brain areas with significantly increased T2 relaxation values—Multiple brain sites in HF subjects showed significantly higher T2 values compared to control subjects, indicating abnormal brain areas. No brain regions emerged with higher T2 values in control subjects compared to HF subjects.

Injury in brain sites associated with ANS control—A major ANS regulatory area, the hypothalamus (Figure 1 C, D, E), was injured. Damage also appeared in primary cortical areas which influence hypothalamic activity (18), modify the baroreflex (19), and alter parasympathetic and sympathetic outflow (20). Cortical autonomic areas affected included the anterior and posterior insular (Figure 2A), anterior, subgeni (Figure 2B) and posterior (Figure 2C) cingulate, and ventral medial prefrontal cortices (Figure 2 B).

Regulatory areas for pain—Regions essential for mediating pain, the raphe magnus (21), as well as the insula (22), increased T2 relaxation values (Figure 1A, B).

Autonomic regulatory areas—The septum (Figure 3A, C), fibers of the fornix (Figure 3B), and an area extending ventrally from the septum to the anterior hypothalamus (Figure 3A, B), important for multiple fluid, thermoregulatory, and sleep maintenance functions (23, 24), showed injury. Portions of the insular cortex, which play a significant role in ANS control (20), also showed tissue damage (Figure 2A).

Injury in brain sites associated with depressive symptoms/depression—Depressed patients without HF show injury in several brain regions (25,26). These regions also appeared injured in our HF subjects, and included the insular cortices (Figure 2A), anterior and subgeni regions of the cingulate cortices (Figure 2B), caudal portion of the ventral medial prefrontal cortex (Figure 2B), hippocampus (Figure 4D), and portions of the cerebellum (Figure 4 E, F).

Injury in brain sites associated with cognition—Brain areas responsible for short-term memory function, including the hippocampus and its output fibers of the fornix, projecting to the septum (27), and to the anterior thalamus (Figure 4B) via the mammillary bodies, were injured. Additionally, the caudate nuclei, which play important roles in cognition and behavioral performance (28), were damaged in the HF subjects (Figure 4 A, C). The anterior and mid portions of the corpus callosum, important for mediating expressive aphasia (29) (a major concern in HF), also were damaged (Figure 3B).

Region-of-interest analyses

Mean T2 relaxation values of HF and control subjects, derived from different brain locations, are summarized in Table 2. All brain sites showed significantly higher T2 relaxation values

(i.e., brain damage) in HF compared to control subjects, and regions with injury are comparable to those determined with voxel-based-relaxometry findings.

Discussion

Overview

Heart failure subjects showed damage to multiple brain regions that play significant roles in ANS control, as well as cognitive function, including memory processing, and pain, language, and mood regulation. Many of the ancillary emotional, language, and cognitive deficits found in HF may derive from these injuries (6,30-31). Previous neuro-imaging studies of HF patients have either used volumetric studies of gray matter and/or total brain volume, or examined infarct frequency and location in white matter. This study differs in using a quantitative T2 relaxometry approach, which assesses the integrity of both gray and white matter, and is more sensitive to neuronal or axonal injury, as opposed to visual examination of tissue infarcts or gray matter volume evaluation.

Autonomic regulation

Classic characteristics of HF include impaired ANS activity, including exaggerated sympathetic tone, excessive catecholamine outflow, impaired dynamic responses to cardiovascular challenges, and altered fluid regulation (32-34). Both the hypothalamus and its cortical regulatory areas, including insular, cingulate and ventral medial prefrontal cortices, were affected. Blood pressure control would be compromised by cerebellar injury, which serves a major role in regulating blood pressure changes to body movement (19).

Other data suggest that CNS functions related to autonomic control are compromised in HF. Brain regions with structural damage found here overlapped brain sites showing impaired functional responses to ANS challenges (cold pressor and Valsalva) and reduced regional gray matter volume in another sample of HF patients (9,34,35). The cingulate and insular cortices normally respond to a variety of autonomic and ventilatory challenges (20,36). Both insular and cingulate cortices have extensive projections to the right ventral medial prefrontal cortex, and all three regions influence the hypothalamus during autonomic challenges (36-38). Injury in any portion of these structures has the potential to modify hypothalamic control of sympathetic outflow and to delay or modify cardiovascular responses to blood pressure challenges, deficits typically found in HF.

Injury in pain regulation, emotional and cognitive areas

Heart failure patients report that control of pain is a significant issue (5). The raphe magnus showed injury here; a principal function of the raphe magnus is to inhibit pain (21). Injury to the raphe magnus would prevent the normal inhibition of pain through periaqueductal gray processes, and may contribute to higher levels of perceived pain in HF patients. In addition, the subgenual cingulate and insular cortices were affected; both structures help to mediate perception of pain (22).

Heart failure patients show a high incidence of depression and/or depressive symptoms (40-60%) (7,39). Depression in non-HF patients is usually accompanied by injury in the insula, cingulate (especially subgenual and anterior portions of the cingulate cortices), and hippocampus, as well as cerebellar/vestibular areas (40-43). The insular, cingulate and frontal cortices, hippocampus, and portions of the cerebellum all showed damage here, which may affect mood in the syndrome. Other emotional signs are found in HF; a high proportion report increased dyspnea (perception of inadequate air/shortness of breath). This neurally-mediated perception that accompanies even minimal physical effort is related to cingulate cortex, insula, and cerebellar function (44,45).

Approximately 80% of HF patients have short-term memory deficits (6). The pattern of injury in the hippocampus, fibers of the fornix, and anterior thalamus shown by T2 relaxometry in HF mirrors the classic damage found in Wernicke-Korsakoff's syndrome (27). Wernicke-Korsakoff's syndrome is associated with severe short-term memory loss and thiamine deficiency, and is typically found in patients with chronic alcoholism. Thiamine deficiency can develop from multiple sources, including use of diuretics, nutritional malabsorption, and dialysis (46), and these factors are frequently encountered in HF. Thus, the potential for selective neural injury in HF developing from thiamine deficiency should not be overlooked.

In addition to short-term memory problems, other cognitive aberrations are also common in HF patients. Attention deficits, difficulty with complex reasoning, and confusion (inability to absorb and retain information) have been reported in up to 80% of HF patients (6,47). The neuropsychological deficits may stem from damage appearing in several brain structures, but the bilateral damage in the caudate nuclei, in particular, would exert prominent cognitive and behavioral effects. The caudate nuclei interacts with multiple brain sites, including thalamic and frontal lobe sites, and mediates major circuitry important for higher cognitive and limbic functions, including pathways to the dorsolateral prefrontal and lateral orbitofrontal cortices (28). Behavioral and learning deficits can be produced by injury to specific areas of prefrontal cortex, but these deficits can also be reproduced with lesions to caudate nuclei (28); thus, the caudate nuclei damage found here likely underlies at least some of the cognitive and other behavioral deficits in HF.

HF subjects showed abnormalities in the genu and rostral portions of the corpus callosum. The corpus callosum, a major fiber bundle between the cerebral hemispheres, contributes to communication and integration of sensory and other information between cortical regions. Injury to rostral portions of the corpus callosum may play a significant role in the frequent anecdotal reports of expressive aphasia in HF patients, as persons without HF and with agenesis of the corpus callosum show significant communication and language difficulties (29).

T2 relaxation values and tissue injury

T2 relaxation values rise with increased free water content in tissue (in the absence of diamagnetic and paramagnetic substances), i.e., increased number of water molecules not bounded to cells. The condition of increased free water content is associated with tissue injury, such as damage to or loss of myelin, axons, or cells (myelin or axonal injury in white matter; cell body or membrane destruction in gray matter) in chronic states. Chronic processes, such as axonal injury, demyelination and gliosis, reduce macromolecules and their associated bound water protons, thereby increasing the presence of free water content in tissue, resulting in higher T2 relaxation values. Although higher T2 relaxation values do not discriminate between injury due to different processes, we can speculate as to likely causes. Abnormalities in brain regions may result from hypoxic/ischemic processes associated with impaired perfusion (secondary to low cardiac output accompanying heart failure) and/or sleep-disordered breathing (commonly reported in HF, range of 40-100%) (48,49). Multiple injurious processes can accompany hypoxia or ischemia, with animal models of intermittent hypoxia, simulating obstructive sleep apnea, inducing injury in cerebellar, hippocampal, frontal cortex, and septal structures (50-55). One hypoxic/ischemic injurious process is that from excitotoxic damage; such a mechanism has been proposed for Purkinje cerebellar cell injury from climbing fibers of the inferior olive (56). Inflammatory processes associated with ischemia (57), depression (58), sleep-disordered breathing (59,60), and HF (61,62) can also contribute to the damage.

Study Limitations

The relatively small sample size is a limitation for this study. However, differences emerged between the groups despite the relatively low number of subjects, demonstrating a very large

effect size on brain injury in the HF subjects. Another limitation of the study sample was that characteristics of our HF subjects (younger age, mostly non-ischemic etiology, relative lack of co-morbidities) do not reflect the demographics of the vast majority of HF patients. Therefore, the findings of this study may not apply to the general population of HF patients. Yet, by selecting HF subjects who had these atypical characteristics, we could control for variables which can alter brain structure (such as age, brain vessel atherosclerotic-induced neural ischemia, and medical co-morbidities). Consequently, the study findings more likely reflect the contribution of HF toward brain injury rather than age, neurovascular atherosclerosis, or other medical conditions. As this study was a one-time evaluation of brain structure (correlational study design), it would be difficult to establish the mechanism(s) which underlie the brain damage. However, we speculate that etiologies for the observed brain injury include hypoperfusion secondary to low cardiac output (not likely the sole source, as no global reduction in HF brain volumes occurred), and abnormal cerebrovascular autoregulation. Alterations in perfusion accompanying sleep-disordered breathing events pose a particular concern. Infarction is an unlikely etiology, as no visible infarctions at the sites of T2 abnormalities in the HF patients were noted.

Conclusions

Structural changes, as indicated by prolonged T2 relaxation values indicative of brain injury, appear in areas involved in autonomic, pain, mood, language, and cognitive function in patients with HF. Brain deficits emerged in the hypothalamus, as well as cerebral cortical structures which regulate the hypothalamus, including the insular, cingulate, and ventral medial prefrontal cortices. Together with deep cerebellar nuclei and cortex, these structures are essential for maintaining ANS control, which is severely affected in HF. A set of these structures, including the insular and cingulate cortices, have been implicated in mediating depressive symptoms in addition to ANS regulatory roles; depressive symptoms are common in HF. Other affected brain regions included the raphé magnus, caudate nuclei, corpus callosum, anterior thalamus, anterior fornix, hippocampus, frontal, parietal, and occipital cortices. Several of these regions, including the hippocampus and its projecting fibers in the fornix, play significant roles in short term memory; the caudate nuclei and prefrontal cortex play additional roles in cognitive function. Both memory and other cognitive capabilities are frequently disturbed in HF subjects. The raphé magnus and insulae are damaged, possibly leading to a loss of inhibition of pain in HF. The processes underlying injury in multiple brain regions are unclear, but may include ischemic/hypoxic, or inflammatory processes. The damage has the potential to exacerbate the HF physiologic symptoms and contribute to neuropsychological and language deficits.

The findings suggest several clinical implications. A patient with HF is likely to show brain injury in areas that affect cognitive, autonomic, and emotional functions, and patients need to be evaluated for such impairments. Behavioral functions disturbed by the injury can impact the patient's ability for self-care; thus, HF patient education/self-management instructional methods may need to be re-evaluated. Of special importance is the need for development of interventions to prevent brain injury in this patient population; the experience from other chronic diseases, such as Wernicke-Korsakoff's syndrome, suggest that aggressive management of nutrients may be useful.

Acknowledgments

We thank Rebecca Harper, Edwin Valladares, Stacy Serber, and Rebecca Cross for assistance with data collection.

Grant support: This research was supported by the National Institute of Nursing Research R01 NR-009116 and by NHLBI-60296.

References

1. Fonarow GC, Yancy CW, Heywood JT. Adherence to heart failure quality-of-care indicators in US hospitals: analysis of the ADHERE Registry. *Arch Intern Med* 2005;165(13):1469–77. [PubMed: 16009861]
2. Thom T, Haase N, Rosamond W, Howard VJ, Rumsfeld J, Manolio T, et al. Heart disease and stroke statistics--2006 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation* 2006;113(6):e85–151. [PubMed: 16407573]
3. Cohn JN, Levine TB, Olivari MT, Garberg V, Lura D, Francis GS, et al. Plasma norepinephrine as a guide to prognosis in patients with chronic congestive heart failure. *N Engl J Med* 1984;311(13):819–23. [PubMed: 6382011]
4. Godfrey C, Harrison MB, Medves J, Tranmer JE. The symptom of pain with heart failure: a systematic review. *J Card Fail* 2006;12(4):307–13. [PubMed: 16679265]
5. Godfrey CM, Harrison MB, Friedberg E, Medves JM, Tranmer JE. The symptom of pain in individuals recently hospitalized for heart failure. *J Cardiovasc Nurs* 2007;22(5):368–74. [PubMed: 17724418] discussion 6–7
6. Almeida OP, Flicker L. The mind of a failing heart: a systematic review of the association between congestive heart failure and cognitive functioning. *Intern Med J* 2001;31(5):290–5. [PubMed: 11512600]
7. Jiang W, Kuchibhatla M, Clary GL, Cuffe MS, Christopher EJ, Alexander JD, et al. Relationship between depressive symptoms and long-term mortality in patients with heart failure. *Am Heart J* 2007;154(1):102–8. [PubMed: 17584561]
8. Schmidt R, Fazekas F, Offenbacher H, Dusleag J, Lechner H. Brain magnetic resonance imaging and neuropsychologic evaluation of patients with idiopathic dilated cardiomyopathy. *Stroke* 1991;22(2):195–9. [PubMed: 2003283]
9. Woo MA, Macey PM, Fonarow GC, Hamilton MA, Harper RM. Regional brain gray matter loss in heart failure. *J Appl Physiol* 2003;95(2):677–84. [PubMed: 12716866]
10. Stromberg A, Martensson J, Fridlund B, Levin LA, Karlsson JE, Dahlstrom U. Nurse-led heart failure clinics improve survival and self-care behaviour in patients with heart failure: results from a prospective, randomised trial. *Eur Heart J* 2003;24(11):1014–23. [PubMed: 12788301]
11. Almeida JR, Alves TC, Wajngarten M, Rays J, Castro CC, Cordeiro Q, et al. Late-life depression, heart failure and frontal white matter hyperintensity: a structural magnetic resonance imaging study. *Braz J Med Biol Res* 2005;38(3):431–6. [PubMed: 15761623]
12. Petropoulos H, Friedman SD, Shaw DW, Artru AA, Dawson G, Dager SR. Gray matter abnormalities in autism spectrum disorder revealed by T2 relaxation. *Neurology* 2006;67(4):632–6. [PubMed: 16924017]
13. Hendry J, DeVito T, Gelman N, Densmore M, Rajakumar N, Pavlosky W, et al. White matter abnormalities in autism detected through transverse relaxation time imaging. *Neuroimage* 2006;29(4):1049–57. [PubMed: 16214373]
14. Radford MJ, Arnold JM, Bennett SJ, Cinquegrani MP, Cleland JG, Havranek EP, et al. ACC/AHA key data elements and definitions for measuring the clinical management and outcomes of patients with chronic heart failure: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Data Standards (Writing Committee to Develop Heart Failure Clinical Data Standards): developed in collaboration with the American College of Chest Physicians and the International Society for Heart and Lung Transplantation: endorsed by the Heart Failure Society of America. *Circulation* 2005;112(12):1888–916. [PubMed: 16162914]
15. Duncan JS, Bartlett P, Barker GJ. Technique for measuring hippocampal T2 relaxation time. *AJNR Am J Neuroradiol* 1996;17(10):1805–10. [PubMed: 8933861]
16. Kumar R, Macey PM, Woo MA, Alger JR, Keens TG, Harper RM. Neuroanatomic deficits in congenital central hypoventilation syndrome. *J Comp Neurol* 2005;487(4):361–71. [PubMed: 15906312]
17. Pell GS, Briellmann RS, Waites AB, Abbott DF, Jackson GD. Voxel-based relaxometry: a new approach for analysis of T2 relaxometry changes in epilepsy. *Neuroimage* 2004;21(2):707–13. [PubMed: 14980573]

18. Craig AD. How do you feel? Interoception: the sense of the physiological condition of the body. *Nat Rev Neurosci* 2002;3(8):655–66. [PubMed: 12154366]
19. Michelini LC. The NTS and integration of cardiovascular control during exercise in normotensive and hypertensive individuals. *Curr Hypertens Rep* 2007;9(3):214–21. [PubMed: 17519128]
20. Oppenheimer SM, Gelb A, Girvin JP, Hachinski VC. Cardiovascular effects of human insular cortex stimulation. *Neurology* 1992;42(9):1727–32. [PubMed: 1513461]
21. Brink TS, Hellman KM, Lambert AM, Mason P. Raphe magnus neurons help protect reactions to visceral pain from interruption by cutaneous pain. *J Neurophysiol* 2006;96(6):3423–32. [PubMed: 16928792]
22. Henderson LA, Gandevia SC, Macefield VG. Somatotopic organization of the processing of muscle and cutaneous pain in the left and right insula cortex: a single-trial fMRI study. *Pain* 2007;128(12):20–30. [PubMed: 17011704]
23. Bernardis LL, Bellinger LL. The lateral hypothalamic area revisited: ingestive behavior. *Neurosci Biobehav Rev* 1996;20(2):189–287. [PubMed: 8811717]
24. Mignot E, Taheri S, Nishino S. Sleeping with the hypothalamus: emerging therapeutic targets for sleep disorders. *Nat Neurosci* 2002;5(Suppl):1071–5. [PubMed: 12403989]
25. Boes AD, McCormick LM, Coryell WH, Nopoulos P. Rostral anterior cingulate cortex volume correlates with depressed mood in normal healthy children. *Biol Psychiatry* 2008;63(4):391–7. [PubMed: 17916329]
26. Cardoner N, Soriano-Mas C, Pujol J, Alonso P, Harrison BJ, Deus J, et al. Brain structural correlates of depressive comorbidity in obsessive-compulsive disorder. *Neuroimage* 2007;38(3):413–21. [PubMed: 17889563]
27. Squire LR. Memory and the hippocampus: a synthesis from findings with rats, monkeys, and humans. *Psychol Rev* 1992;99(2):195–231. [PubMed: 1594723]
28. Naismith S, Hickie I, Ward PB, Turner K, Scott E, Little C, et al. Caudate nucleus volumes and genetic determinants of homocysteine metabolism in the prediction of psychomotor speed in older persons with depression. *Am J Psychiatry* 2002;159(12):2096–8. [PubMed: 12450963]
29. Friederici AD, von Cramon DY, Kotz SA. Role of the corpus callosum in speech comprehension: interfacing syntax and prosody. *Neuron* 2007;53(1):135–45. [PubMed: 17196536]
30. Antonelli Incalzi R, Trojano L, Acanfora D, Crisci C, Tarantino F, Abete P, et al. Verbal memory impairment in congestive heart failure. *J Clin Exp Neuropsychol* 2003;25(1):14–23. [PubMed: 12607168]
31. Bennett SJ, Sauve MJ. Cognitive deficits in patients with heart failure: a review of the literature. *J Cardiovasc Nurs* 2003;18(3):219–42. [PubMed: 12837012]
32. Floras JS. Sympathetic activation in human heart failure: diverse mechanisms, therapeutic opportunities. *Acta Physiol Scand* 2003;177(3):391–8. [PubMed: 12609011]
33. Notarius CF, Spaak J, Morris BL, Floras JS. Comparison of muscle sympathetic activity in ischemic and nonischemic heart failure. *J Card Fail* 2007;13(6):470–5. [PubMed: 17675061]
34. Woo MA, Macey PM, Keens PT, Kumar R, Fonarow GC, Hamilton MA, et al. Functional abnormalities in brain areas that mediate autonomic nervous system control in advanced heart failure. *J Card Fail* 2005;11(6):437–46. [PubMed: 16105635]
35. Woo MA, Macey PM, Keens PT, Kumar R, Fonarow GC, Hamilton MA, et al. Aberrant central nervous system responses to the Valsalva maneuver in heart failure. *Congest Heart Fail* 2007;13(1):29–35. [PubMed: 17272960]
36. Critchley HD. Neural mechanisms of autonomic, affective, and cognitive integration. *J Comp Neurol* 2005;493(1):154–66. [PubMed: 16254997]
37. Critchley HD, Mathias CJ, Josephs O, O'Doherty J, Zanini S, Dewar BK, et al. Human cingulate cortex and autonomic control: converging neuroimaging and clinical evidence. *Brain* 2003;126(Pt 10):2139–52. [PubMed: 12821513]
38. Kimmerly DS, O'Leary DD, Menon RS, Gati JS, Shoemaker JK. Cortical regions associated with autonomic cardiovascular regulation during lower body negative pressure in humans. *J Physiol* 2005;569(Pt 1):331–45. [PubMed: 16150800]

39. Rumsfeld JS, Havranek E, Masoudi FA, Peterson ED, Jones P, Tooley JF, et al. Depressive symptoms are the strongest predictors of short-term declines in health status in patients with heart failure. *J Am Coll Cardiol* 2003;42(10):1811–7. [PubMed: 14642693]
40. Keedwell PA, Andrew C, Williams SC, Brammer MJ, Phillips ML. The neural correlates of anhedonia in major depressive disorder. *Biol Psychiatry* 2005;58(11):843–53. [PubMed: 16043128]
41. Agid R, Levin T, Gomori JM, Lerer B, Bonne O. T2-weighted image hyperintensities in major depression: focus on the basal ganglia. *Int J Neuropsychopharmacol* 2003;6(3):215–24. [PubMed: 12974987]
42. Haas BW, Omura K, Constable RT, Canli T. Emotional conflict and neuroticism: personality-dependent activation in the amygdala and subgenual anterior cingulate. *Behav Neurosci* 2007;121(2):249–56. [PubMed: 17469914]
43. Marchand WR, Lee JN, Thatcher GW, Jensen C, Stewart D, Dilda V, et al. A functional MRI study of a paced motor activation task to evaluate frontal-subcortical circuit function in bipolar depression. *Psychiatry Res* 2007;155(3):221–30. [PubMed: 17588725]
44. Banzett RB, Mulnier HE, Murphy K, Rosen SD, Wise RJ, Adams L. Breathlessness in humans activates insular cortex. *Neuroreport* 2000;11(10):2117–20. [PubMed: 10923655]
45. Peiffer C, Poline JB, Thivard L, Aubier M, Samson Y. Neural substrates for the perception of acutely induced dyspnea. *Am J Respir Crit Care Med* 2001;163(4):951–7. [PubMed: 11282772]
46. Harper C. Thiamine (vitamin B1) deficiency and associated brain damage is still common throughout the world and prevention is simple and safe! *Eur J Neurol* 2006;13(10):1078–82. [PubMed: 16987159]
47. Zuccala G, Marzetti E, Cesari M, Lo Monaco MR, Antonica L, Cocchi A, et al. Correlates of cognitive impairment among patients with heart failure: results of a multicenter survey. *Am J Med* 2005;118(5):496–502. [PubMed: 15866252]
48. Ferrier K, Campbell A, Yee B, Richards M, O'Meeghan T, Weatherall M, et al. Sleep-disordered breathing occurs frequently in stable outpatients with congestive heart failure. *Chest* 2005;128(4):2116–22. [PubMed: 16236863]
49. Javaheri S, Parker TJ, Liming JD, Corbett WS, Nishiyama H, Wexler L, et al. Sleep apnea in 81 ambulatory male patients with stable heart failure. Types and their prevalences, consequences, and presentations. *Circulation* 1998;97(21):2154–9. [PubMed: 9626176]
50. Gozal D, Daniel JM, Dohanich GP. Behavioral and anatomical correlates of chronic episodic hypoxia during sleep in the rat. *J Neurosci* 2001;21(7):2442–50. [PubMed: 11264318]
51. Veasey SC, Davis CW, Fenik P, Zhan G, Hsu YJ, Pratico D, Gow A. Long-term intermittent hypoxia in mice: protracted hypersomnolence with oxidative injury to sleep-wake brain regions. *Sleep* 2004;27(2):194–201. [PubMed: 15124711]
52. Pae EK, Chien P, Harper RM. Intermittent hypoxia damages cerebellar cortex and deep nuclei. *Neurosci Lett* 2005;375(2):123–8. [PubMed: 15670654]
53. Caples SM, Garcia-Touchard A, Somers VK. Sleep-disordered breathing and cardiovascular risk. *Sleep* 2007;30(3):291–303. [PubMed: 17425225]
54. Javaheri S, Shukla R, Zeigler H, Wexler L. Central sleep apnea, right ventricular dysfunction, and low diastolic blood pressure are predictors of mortality in systolic heart failure. *J Am Coll Cardiol* 2007;49(20):2028–34. [PubMed: 17512359]
55. Welsh JP, Yuen G, Placantonakis DG, Vu TQ, Haiss F, O'Hearn E, et al. Why do Purkinje cells die so easily after global brain ischemia? Aldolase C, EAAT4, and the cerebellar contribution to posthypoxic myoclonus. *Adv Neurol* 2002;89:331–59. [PubMed: 11968459]
56. O'Hearn E, Molliver ME. The olivocerebellar projection mediates ibogaine-induced degeneration of Purkinje cells: a model of indirect, trans-synaptic excitotoxicity. *J Neurosci* 1997;17(22):8828–41. [PubMed: 9348351]
57. Teramoto S, Yamamoto H, Ouchi Y. Increased C-reactive protein and increased plasma interleukin-6 may synergistically affect the progression of coronary atherosclerosis in obstructive sleep apnea syndrome. *Circulation* 2003;107(5):E40–0. [PubMed: 12578892]
58. Gold SM, Irwin MR. Depression and immunity: inflammation and depressive symptoms in multiple sclerosis. *Neurol Clin* 2006;24(3):507–19. [PubMed: 16877121]

59. Bravo Mde L, Serpero LD, Barcelo A, Barbe F, Agusti A, Gozal D. Inflammatory proteins in patients with obstructive sleep apnea with and without daytime sleepiness. *Sleep Breath* 2007;11(3):177–85. [PubMed: 17279423]
60. Phillips CL, Yang Q, Williams A, Roth M, Yee BJ, Hedner JA, et al. The effect of short-term withdrawal from continuous positive airway pressure therapy on sympathetic activity and markers of vascular inflammation in subjects with obstructive sleep apnoea. *J Sleep Res* 2007;16(2):217–25. [PubMed: 17542952]
61. Ratnasamy C, Kinnamon DD, Lipshultz SE, Rusconi P. Associations between neurohormonal and inflammatory activation and heart failure in children. *Am Heart J* 2008;155(3):527–33. [PubMed: 18294492]
62. Windram JD, Loh PH, Rigby AS, Hanning I, Clark AL, Cleland JG. Relationship of high-sensitivity C-reactive protein to prognosis and other prognostic markers in outpatients with heart failure. *Am Heart J* 2007;153(6):1048–55. [PubMed: 17540208]

Figure 1.

Injury in the raphé magnus in sagittal (A, arrow) and axial (B, arrow) views. Injury also appears in the hypothalamus [arrows, C (coronal), D (sagittal), and E (axial) views]. Areas of injury are color-coded for level of significance (color scale t values). L= left, R= right side of brain; X, Y and Z values represent lateral distance in mm from midline, dorsal-ventral, and rostral-caudal from the anterior commissure, respectively. For all figures, the injury is presented as a group/averaged for HF vs. Control subjects.

Figure 2.

Injury in cortical regions which influence hypothalamic outflow. The right anterior insula, left posterior insula (A), anterior cingulate, subgenus of anterior cingulate (bordering caudal corpus callosum), caudal ventral medial prefrontal cortex (B), and posterior cingulate (C), arrows, were affected. Figure conventions as in Figure 1.

Figure 3.

Injury appeared in a region extending from the left and right caudate nuclei through the internal capsule (A), fornix (B, vertical solid arrow), and septum (A, C) to the anterior hypothalamus (A, B). Injury also appears in the anterior and mid-corpus callosum (B, dashed blue arrow). Figure conventions as in Figure 1.

Figure 4. Areas of injury in the left and right caudate (A, C), anterior thalamus (B), posterior hippocampus (D), and cerebellar cortex (E, F). Figure conventions as in Figure 1.

Table 1
Demographic Data

Variables	Heart Failure N = 13	Controls N = 49	p-value
Mean age $\pm$ SD (years)	54.6 $\pm$ 8.3	50.6 $\pm$ 7.3	0.09
Gender (males)	9 (69%)	29 (59%)	0.51
Handedness (right)	12 (92%)	39 (80%)	0.29
Mean BMI $\pm$ SD (kg/m ²)	28.8 $\pm$ 6.3	25.3 $\pm$ 4.8	0.03
Mean LVEF $\pm$ SD	0.28 $\pm$ 0.07	---	---
Electrocardiogram			
Sinus rhythm	11 (85%)	49 (100%)	0.005
Atrial fibrillation	2 (15%)	0	
HF etiology		---	---
Ischemic	6 (46%)		
Non-ischemic	7 (54%)		

SD = Standard deviation; BMI = Body mass index; LVEF = Left ventricular ejection fraction.

Table 2
Mean T2-relaxation values of different brain regions of HF and control subjects.

Brain regions	T2-relaxation values (Mean $\pm$ SD, in ms)		Voxels (8 mm ³)	p values [A] vs. [B]	Figures
	Controls (n = 49) [A]	HF (n = 13) [B]			
Ant. fornix	229.23 $\pm$ 28.42	276.34 $\pm$ 42.15	29	< 0.001	Fig. 3A-C
Cerebellar vermis	159.55 $\pm$ 19.74	185.06 $\pm$ 23.42	96	< 0.002	—
Genu of cingulate ext. to vent. med. prefrontal cortex	135.24 $\pm$ 12.74	152.35 $\pm$ 13.42	96	< 0.001	Fig. 2B
Left ant. frontal cortex	221.38 $\pm$ 23.53	246.23 $\pm$ 7.86	6	< 0.003	—
Left ant. insula	184.51 $\pm$ 21.57	210.54 $\pm$ 28.62	4	< 0.001	—
Left ant. thalamus ext. to ant. hypothalamus	134.83 $\pm$ 16.86	159.16 $\pm$ 26.69	224	< 0.001	Fig. 1C-E; Fig. 4B
Left cau. cerebellar cortex	130.65 $\pm$ 12.30	147.43 $\pm$ 24.00	29	< 0.009	—
Left caudate nuclei	176.11 $\pm$ 21.95	207.37 $\pm$ 33.87	108	< 0.001	Fig. 4A
Left dor. frontal cortex	214.76 $\pm$ 16.97	239.63 $\pm$ 15.68	57	< 0.001	—
Left med. frontal cortex ext. to ant. cingulate	183.57 $\pm$ 18.44	207.92 $\pm$ 20.56	62	< 0.001	—
Left occipital cortex	103.47 $\pm$ 6.06	110.50 $\pm$ 5.64	21	< 0.001	—
Left parietal cortex ext. to sup. temporal cortex	142.62 $\pm$ 16.53	171.72 $\pm$ 22.37	184	< 0.001	—
Left post. insula	113.49 $\pm$ 10.53	127.22 $\pm$ 15.68	38	< 0.001	Fig. 2A
Left rost. to midbody of corpus callosum	173.50 $\pm$ 21.18	203.60 $\pm$ 30.27	113	< 0.001	—
Left vent. cerebellar cortex	134.82 $\pm$ 12.61	152.83 $\pm$ 16.65	179	< 0.002	Fig. 4E, F
Left vent. cau. cerebellar cortex	120.62 $\pm$ 9.70	133.31 $\pm$ 18.11	23	< 0.002	—
Raphé magnus	126.34 $\pm$ 6.19	134.20 $\pm$ 9.05	46	< 0.008	Fig. 1A, B
Preoptic hypothalamus	167.05 $\pm$ 22.65	195.88 $\pm$ 31.68	38	< 0.001	—
Right ant. cingulate	194.60 $\pm$ 22.48	221.88 $\pm$ 22.26	8	< 0.001	Fig. 2B
Right ant. frontal cortex	166.15 $\pm$ 16.43	187.05 $\pm$ 22.95	7	< 0.001	—
Right ant. insula	121.93 $\pm$ 10.76	137.05 $\pm$ 19.51	30	< 0.001	Fig. 2A
Right ant. thalamus ext. to ant. hypothalamus	168.68 $\pm$ 26.50	202.96 $\pm$ 33.84	55	< 0.001	—
Right cau. cerebellar cortex	131.88 $\pm$ 12.55	150.58 $\pm$ 25.19	40	< 0.003	—
Right caudate nuclei	184.36 $\pm$ 24.76	214.35 $\pm$ 26.94	46	< 0.001	Fig. 4C
Right dor. surface of temporal cortex	155.15 $\pm$ 13.29	174.96 $\pm$ 13.66	92	< 0.001	—
Right dor. ant. frontal cortex	204.08 $\pm$ 15.43	230.79 $\pm$ 17.41	226	< 0.001	—
Right dor. frontal cortex	221.41 $\pm$ 19.81	243.54 $\pm$ 16.49	10	< 0.004	—

Brain regions	T2-relaxation values (Mean $\pm$ SD, in ms)		Voxels (8 mm ³)	p values [A] vs. [B]	Figures
	Controls (n = 49) [A]	HF (n = 13) [B]			
Right dor. med. cerebellar cortex	148.79 $\pm$ 22.71	180.67 $\pm$ 30.96	108	< 0.001	—
Right med. occipital cortex	114.07 $\pm$ 9.25	125.92 $\pm$ 15.21	6	< 0.002	—
Right occipital cortex	120.52 $\pm$ 13.70	139.20 $\pm$ 23.64	16	< 0.001	—
Right parietal cortex	138.42 $\pm$ 15.56	161.46 $\pm$ 34.35	11	< 0.001	—
Right post. cingulate	120.96 $\pm$ 12.56	137.23 $\pm$ 21.35	8	< 0.001	—
Right post. hippocampus and surrounding white matter	116.10 $\pm$ 8.80	132.44 $\pm$ 14.44	2329	< 0.001	Fig. 4D
Right rost. to midbody of corpus callosum	181.91 $\pm$ 24.01	215.05 $\pm$ 32.64	125	< 0.001	—
Right vent. cerebellar cortex	110.09 $\pm$ 6.18	117.48 $\pm$ 8.36	8	< 0.004	—
Right vent. frontal cortex	121.11 $\pm$ 8.66	132.80 $\pm$ 13.51	14	< 0.001	—

Table legend: Ant., Anterior; Vent., Ventral; Med., Medial; Cau., Caudal; Dor., Dorsal; Sup., Superior; Post., Posterior; Ext., Extending; Rost., Rostrum; Dor., Dorsal.