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Regional Hippocampal Damage in Heart Failure

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Abstract

Aims—Heart failure (HF) patients show cognitive and mood impairments, including short-term memory loss and depression, adversely impacting quality of life and self-care management. Brain regions, including the hippocampus, a structure significantly involved in memory and mood, show injury in HF, but the integrity of specific hippocampal subregions is unclear.

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Conflict of Interest

No authors have any conflicts of interest to disclose.

Methods and results—To assess regional hippocampal volume loss, we evaluated 17 HF patients (mean age $\pm$ SD, 54.4 ± 2.0 years; 12 male, LVEF $28.3 \pm 6.8\%$; NYHA Class II/III 94%/6%) and 34 healthy control subjects (52.3 ± 1.3 years; 24 male) using high-resolution T1-weighted magnetic resonance imaging and evaluated localized surface changes with morphometric procedures. Hippocampi were manually outlined, and volumes calculated from normalized tracings.

Volume differences between groups were assessed by two-sample t-tests, and regional differences were assessed by surface morphometry. HF patients exhibited smaller hippocampal volumes than controls (Right: 3060 ± 146 vs. 3478 ± 94 mm³; $p = 0.02$, Left: 3021 ± 145 vs. 3352 ± 98 mm³; $p = 0.06$). Volume reductions were detected principally in CA1, an area integral to an array of learning and memory functions, as well as in mid- to posterior CA3 and subiculum.

Conclusion—The hippocampus shows regional volume reduction in HF, which may contribute to short-term memory loss and depression associated with the condition.

Keywords

Magnetic resonance imaging; brain; hippocampus; memory; cognition

Introduction

Heart failure (HF) patients exhibit a wide range of cognitive and mood problems, including short-term memory deficits, depression, and anxiety,^{1, 2} characteristics that indicate the presence of central nervous system dysfunction and which may be related to neural injury, and specifically to damage of the hippocampus, a brain structure integrally involved in such neuropsychological functions.^{3–6} The hippocampus is also a very vascular structure and is one of the most vulnerable brain regions to changes in blood flow and hypoxemia, both common co-morbidities during HF exacerbations.^{4, 6} Whole-brain magnetic resonance imaging (MRI) indicates regionally-compromised neural structure in HF patients,^{5, 6} with extensive injury occurring in a number of limbic brain regions, including the hippocampus, insular and cingulate cortices, and mammillary bodies.^{6, 7} However, technical limitations of whole-brain analysis techniques preclude precise quantification of structural changes within specific brain structures, such as the hippocampus.

A precise description of structural changes within the hippocampus may also provide insight into the specific anatomical abnormalities accompanying HF. The hippocampal formation consists of several subregions, including the dentate gyrus, subiculum, and cornu Ammonis, which has four subdivisions (CA1–CA4). The CA1 subfield is critical for encoding novel information,⁸ and in conjunction with CA3, enables consolidation and retrieval of memory.⁴ Neuroimaging studies show that reduced hippocampal volume in CA1 and in the subiculum is associated with compromised memory performance in patients with mild cognitive impairment.³ Injury in these specific hippocampal regions may contribute to the memory deficits found in HF. However, an evaluation of hippocampal subregions, which requires localization of volume loss, has not been reported in HF.

Our objective was to quantify and localize differences in hippocampal volume between patients with HF and healthy control subjects, using surface morphometry procedures. We hypothesized that HF patients would show volume reductions in the CA1 region of the hippocampus.

Methods

2.1 Subjects

Seventeen HF (mean age $\pm$ SD, 54.4 ± 2.0 years; 12 males; left ventricular ejection fraction $28.3 \pm 6.8\%$; New York Heart Association Functional Class II/III 94%/6%) and 34 control subjects (age, 52.3 ± 1.3 years; 24 males) were studied. This group of subjects overlapped those used in a previous study demonstrating mammillary body and fornix fiber injury.⁷ Heart failure diagnoses were made based on national diagnostic criteria.⁹ Patients were recruited from the Ahmanson-University of California at Los Angeles (UCLA) Cardiomyopathy Center and from the Los Angeles community. Inclusion criteria for the HF subjects included systolic, dilated cardiomyopathy and left ventricular ejection fraction < 0.40 . None of the HF patients had evidence or history of alcohol-induced cardiomyopathy or diastolic failure, nor could they have current diabetes, smoking, or hypertension. These inclusion/exclusion criteria were implemented to increase homogeneity of the HF group and decrease risks for other factors which are known to be associated with brain injury. Treatment for HF patients included angiotensin receptor blockers or angiotensin-converting enzyme inhibitors, beta-blockers, and diuretics, with cardiac medications titrated to specific hemodynamic goals.¹⁰ Body weight and medication doses were stable for at least six months prior to the MRI studies. In addition, subjects were able to remain supine throughout the scan without symptoms of dyspnea and without jugular venous distension. Control subjects were age- and gender-matched to the HF subjects (at a 1 HF: 2 Controls ratio) and had no clinical history of cardiovascular disease, stroke, respiratory deficits, or neurological disorders, and were recruited from the greater Los Angeles area. Exclusion criteria for both HF and control subjects included claustrophobia, non-removable metallic devices (such as braces, embolic coils, pacemakers/implantable cardioverter-defibrillators, and stents), inability to lay supine, and body weight exceeding 125 kg, due to MRI scanner limitations. The study protocol was approved by UCLA's Institutional Review Board, and all subjects provided written informed consent prior to the study.

2.2 Magnetic Resonance Imaging

Brain imaging was performed using a 3.0 Tesla MRI scanner (Magnetom Tim-Trio; Siemens, Erlangen, Germany) with an 8-channel head coil. Movement was reduced by way of foam pads on both sides of the head, and subjects remained supine during the scans. Two high-resolution T1-weighted image volumes, covering the entire brain, were collected using a magnetization prepared rapid acquisition gradient echo pulse sequence (MPRAGE) [repetition-time (TR) = 2200 ms; echo-time (TE) = 2.2 ms; inversion-time = 900 ms; flip-angle = 9° ; matrix size = 256×256 ; field of view (FOV) = 230×230 mm; slice thickness = 1.0 mm]. Whole brain proton-density (PD) and T2-weighted images (TR = 10,000 ms; TE1, TE2 = 17, 134 ms; FA = 130° ; matrix size = 256×256 ; FOV = 230×230 mm; slice thickness = 4.0 mm) were also collected. Scanning was repeated if motion was detected.

2.2.1 Evaluation and Preprocessing of the Anatomical Images—The T1-, T2-, and PD-weighted images were visually evaluated to ensure the absence of movement artifacts or gross pathology, such as infarcts or mass lesions. Images were prepared for hippocampal tracing using 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. The two image volumes for each subject were realigned and averaged to improve signal-to-noise ratios. Intensities were corrected for bias due to magnetic field inhomogeneity using the “unified segmentation” procedure. Bias-corrected images were rigid-body aligned to common Montreal Neurological Institute (MNI) space, and resampled at $0.9 \times 0.9 \times 0.9$ mm. A 9-parameter affine transformation (shift, rotate, scale) of each subject’s image to the MNI space was calculated, to correct for variations in brain size across subjects.

2.2.2 Hippocampal Tracing and Volume Quantification—One investigator, blinded to subject diagnosis, performed left and right hippocampal tracings on the reoriented and resampled T1-weighted images in all subjects. The structures were outlined in MRIcroN software using established protocols,^{11, 12} with reference to a neuroanatomic atlas. Initial coronal tracings were followed by refinement of the boundaries in the sagittal plane. Each hippocampal tracing included the hippocampus proper (CA1–CA4), dentate gyrus, and subiculum. Hippocampal volumes were calculated as the sum of all voxels multiplied by voxel volume, based on affine-transformed images (*i.e.*, corrected for head size).

A second investigator re-traced left and right hippocampi of 17 HF and seven control subjects, from which inter-rater reliabilities were calculated for the two investigators. Reliability of volume measurements was calculated using Cronbach’s alpha, a type of intra-class correlation (ICC). Reliability of regional tracing was assessed using the Dice Similarity Coefficient (DSC), an index of the number of overlapping voxels relative to the average total number of voxels, where 0 indicates no overlap and 1 indicates 100% overlap.

2.3 Statistical Analysis

The left and right global hippocampal volumes were compared between groups using independent samples t-tests (in MATLAB, The MathWorks, Inc., Natick, MA). Chi-square and independent samples t-tests were used to compare demographic variables between HF and control subjects. The tests were two-tailed, with significance levels set at $p < 0.05$.

2.3.1 Three Dimensional Surface Morphometry—To determine the distribution of volume loss across hippocampal subfields, hippocampal surface morphometry was performed using radial distance mapping, which evaluates atrophy on the surface based on the underlying thickness of the structure.^{13, 14} A “medial curve,” a line along the center of the hippocampus in the anterior-posterior direction, was calculated as the center of mass of each coronal cross-section. A three-dimensional mesh of the surface was created, based on normalization of surface points of each hippocampal tracing to a fixed number of equally spaced points (30,000). A measurement of thickness was defined at each mesh point as the distance to the medial curve. Between-group differences were assessed at each surface point using two-sample t-tests, and differences were displayed (“mapped”) as color-coded

significance levels on the average 3D hippocampal surface across all subjects. In addition to maps showing areas of statistically significant thickness differences, an indication of effect size, the ratio of mean radial distance in patients relative to controls, was also calculated. This procedure allows visualization of those areas containing the most extensive atrophy, irrespective of variability among subjects.

Results

3.1 Demographics

Demographic data and other variables are summarized in Table 1. Body mass index was significantly greater in HF over control subjects, but no significant differences in age or sex emerged between groups. Approximately half subjects of each group (HF, controls) were White, with the remaining 50% primarily Hispanic and Asians, which was representative of the diverse ethnic population of the city of Los Angeles, California, USA.

3.2 Tracing Reliability

The second investigator traced 17 HF and seven control subjects' left and right hippocampi. Inter-rater reliabilities for global volumes were ICC (left hippocampus) = 0.79 (mean) [0.50, 0.91] (95% confidence intervals), ICC (right) = 0.82 [0.59, 0.92], and regional inter-rater reliabilities were DSC (left hippocampi) = 0.80 (mean) [0.79, 0.81] (95% confidence intervals), DSC (right) = 0.81 [0.79, 0.82].

3.3 Global Volumes

While no differences emerged in whole brain volumes between groups, the HF patients showed a reduction in right hippocampal volume in comparison to healthy controls ($p=0.02$; Table 1). Differences in the left hippocampal volumes between HF and control subjects were of similar magnitude, but were not statistically significant ($p=0.06$; Table 1). The distribution of hippocampal volumes across control and HF groups is illustrated in Figure 1.

3.4 Regional Volumes

The morphometry measures demonstrated statistically significant local volume differences in a number of regions within the hippocampus in the HF subjects, as shown by the significance maps (Fig. 2). The most pronounced declines appeared along the lateral aspect of the hippocampus, which contains the CA1 region (Fig. 2c–e, h). Significant declines were also observed in the medial hippocampus, representing and CA3, with possible minor involvement of the dentate gyrus (Figs. 2a, b), and in the anterior subiculum/presubiculum (Fig. 2f, g). The ratio maps demonstrate the effect size of the atrophy across the entire hippocampal surface (Fig. 3). These maps show the location and extent of atrophy in the patient group relative to the average of the controls.

3.5 Impact of BMI on Hippocampal Volumes

When BMI was used as a covariate in ANCOVA analyses of hippocampal volumes comparing HF and controls, there was no longer any statistical difference between the groups.

Discussion

Heart failure patients showed reduced global hippocampal volumes relative to control subjects, and these volume losses were localized in specific regions, principally CA1, and to a lesser extent, the subiculum. The mechanisms of damage are unclear, but may include several processes, some resulting from perfusion, inflammation, other aspects of HF (duration of disease), and additional factors stemming from comorbidities accompanying the condition (atrial fibrillation, stroke, sleep apnea). Only one of our HF subjects had atrial fibrillation, there were two with a history of sleep apnea (which were discovered after our MRI study) and none had a history of stroke. Also, we did not see evidence of stroke on the MRI scans in any of our study subjects. However, the small number of subjects with comorbidities which may have influenced these findings limited our ability to assess their impact on our statistical analyses.

4.1 Regional specificity

The pattern of the localized volume loss in the hippocampus may indicate specific mechanisms of damage. The CA1 region was preferentially affected, which suggests excitotoxic damage from hypoperfusion and/or obesity. The CA1 area is highly susceptible to hypoxic/ischemic processes, due in part to the glutamate receptor-mediated mitochondrial calcium overload occurring with such challenges, and the demonstrated sensitivity of CA1 neurons to excessive afferent activation.¹⁵ The right hippocampus demonstrates greater volume loss than the left, which may be due, in part, to a relatively small sample size. However, this trend may also reflect preferential right-sided activation for sympathetic regulation, thus being more metabolically demanding of perfusion, which may be unmet by compromised cerebral autoregulation in HF. Localized perfusion, indeed, is compromised in HF.¹⁶ Alternatively, blood oxygen level dependent MRI signals during memory encoding are preferentially decreased in the right anterior hippocampus following interference with slow wave sleep¹⁷ Such disturbances are common in HF¹⁸ and may lead to decreased oxygenation in the right hippocampus during high metabolic demand.

4.2 Relationship of Hippocampal Damage to Other Brain Structures

The hippocampal volume loss may impact other structures that receive input from the hippocampus. Voxel-based morphometry in HF shows overall reduced gray matter volume in the parahippocampal gyrus,¹⁹ a region that communicates directly with the hippocampus proper. Tissue damage within the posterior hippocampus, and white matter changes within the fornix of HF patients were previously shown by voxel-based relaxometry.⁶ The fornix, which is constituted from fibers of the hippocampus, projects to the mammillary bodies, which serve vital roles for learning and memory. Detailed examination of high-resolution anatomical scans shows reduced volume of the mammillary bodies and fornix fibers, in an overlapping HF population.⁷ The fornix injury likely results, in part, from damaged hippocampal neurons that give rise to the fibers; additionally, the fornix fiber loss was greater on the right side, which is consistent with the greater tissue damage in the right hippocampus observed here.

4.3 Potential Mechanisms of Injury

Several processes likely contribute to the hippocampal injury, including cerebrovascular regulatory impairments, cerebral infarction, comorbidities (such as diabetes, obesity, or cerebrovascular autoregulation), and chronic inflammation, although the relative contribution of each mechanism cannot be ascertained from these study data. Unfortunately, we did not have sufficient numbers of subjects with these co-morbidities nor did we have measures of their cognitive or mood/emotional status. It would greatly expand the science if future studies added these factors to their analyses of brain structure in HF. Patients with HF show abnormal cerebrovascular autoregulation and diminished cerebral perfusion.^{16, 20} These decreases in global and regional blood flows can contribute to an ischemic/hypoxic environment, leading to neuronal and glial damage in the hippocampus.²¹ Other common sources of hypoxia in HF include pulmonary edema, anemia, and sleep disordered breathing (both central and obstructive sleep apnea).^{22, 23} Apnea-related hypoxia is associated with injury to multiple structures, including the hippocampus.²⁴ Hippocampal lacunar infarcts are commonly associated with HF at postmortem assessment,²⁵ and could contribute to the volume changes quantified here. However, we did not detect hippocampal infarction in our subjects. Chronic inflammation, possibly associated with obesity, which is present in HF as indicated by elevated levels of pro-inflammatory cytokines in the myocardium and plasma,²⁶ is also associated with neurotoxicity. Another potential source of hippocampal damage seen in our HF subjects is dietary inadequacies, especially thiamine, due to malabsorption, diminished nutritional intake, or high fluid loss secondary to diuretic use. In other diseases with such nutrient deficiencies, brain areas serving memory (such as the hippocampus, mammillary bodies, fornix, and caudate) show injury.²⁷ All of these mechanisms of injury have been reported in HF patients,²⁸ but their relative contribution to the structural change in the hippocampus cannot be ascertained using the present data.

4.3 Study Limitations

While our study findings are interesting, the investigation did have some important limitations. Our HF sample was primarily collected from a specialized heart failure/heart transplant center and our study inclusion criteria for these subjects were dilated, systolic HF, age 40–60 years, no diabetes or hypertension, and an LVEF < 0.40. Therefore, our sample was younger than the average HF patient, did not have common HF co-morbidities, and not representative of HF patients who have preserved ejection fraction or persons with NYHA functional class I or IV. In addition, we were unable to have sufficient numbers of subjects with adequate statistical power to control for important co-morbidities (such as atrial fibrillation, sleep apnea, etc.) in our analyses.

It is also important to remember that there are other brain regions which are damaged in HF and associated with cognition and mood, such as the frontal cortex, insular lobes, and amygdala, as described earlier in the same HF subjects by other MRI procedures. However, this study was designed to examine global and regional hippocampal changes only. While we have these images, we are still in the process of measuring the volumes of these structures.

4.5 Clinical Implications

The damage shown here in hippocampal regions, as well as injury in hippocampal-mammillary body circuitry, likely contribute to cognitive and mood deficits in HF. The affected pathways form an essential part of short-term memory processing, sending fibers to the anterior and dorsal thalamus; damage to this pathway occurs in anterograde and other memory deficiencies.²⁹ Cognitive impairment and depressed mood can impede self-care and quality of life in persons with HF. The hippocampal damage provides a structural explanation for the cognitive and mood abnormalities commonly reported in HF. Moreover, treatments must be explored to protect, prevent, and intervene for brain damage in this group.

4.5 Conclusions

Hippocampal damage appears in HF, predominantly in the CA1 subregion, suggesting that memory circuitry may be especially impacted by the neural injury. The consequences of this hippocampal tissue loss, together with injury to the remaining memory circuitry, may impair anterograde and spatial memory functions, and provide a neuroanatomical basis for some of the mood disturbances commonly found in HF.³⁰ The identification and development of interventions will be essential to help attenuate the deficits that may result from structural alterations to the hippocampus. Potential interventions to provide neuroprotection and/or to encourage neuroplasticity in this region and have been explored in persons after stroke or traumatic brain injury, but have not been used for this purpose in HF, include medications (specifically, statins),³³ exercise,³⁴ and memory/brain exercises.^{35–37} Treatment plans should both consider neuroprotective strategies, and account for impaired cognitive and emotional functioning in HF patients.

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Figure 1. Scatter plot demonstrates individual left and right hippocampal volumes in control (x) and HF (o) subjects. The right hippocampal volumes differed significantly between groups.

Figure 2.

Significance maps of the right and left hippocampus demonstrate localized regions of significant change in HF subjects relative to control subjects. The white regions correspond to those areas with the most significant change ($p < 0.01$). Significant declines appeared in the anterior medial hippocampus (Fig.2a), as well as in the subiculum and CA3, with possible minor involvement of the dentate gyrus (Fig.2b). The most pronounced declines appeared along the lateral aspect of the hippocampus, which contains the CA1 region (Fig. 2c–e, h). A small region of anterior subiculum/presubiculum also exhibited significant differences (Fig.2f, g).

Figure 3.

Ratio maps display color-coded ratios of mean radial distance, in patients relative to controls, and demonstrate specific areas of atrophy and the relative magnitude of HF atrophy in each area. The right side exhibits more extensive atrophy than the left hippocampus. Areas of red and orange represent the most severe local volume loss, and are spatially distributed in a pattern similar to that of the significance maps of Figure 2.

Table 1

Characteristics of 17 HF patients and 34 controls; BMI = body mass index.

	HF N = 17 <i>Mean ± SE</i>	CONTROL N = 34 <i>Mean ± SE</i>	P
Age (years)	54.4 ± 2.0	52.3 ± 1.3	0.38
BMI (kg/m ²)	29.4 ± 1.4	24.8 ± 0.6	0.001
Sex	5♀, 12♂	10♀, 24♂	1.00
Handedness	16 right, 1 left	27 right, 6 left, 1 both	0.38
Left Hippocampal Volume* (mm ³)	3021 ± 145	3352 ± 98	0.06
Right Hippocampal Volume* (mm ³)	3060 ± 146	3478 ± 94	0.02
Total Brain Volume (L)	1.15 ± 0.03	1.17 ± 0.02	0.61

* Hippocampal volumes have been normalized for individual differences in brain size using 9-parameter affine transformation.