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Mammillary bodies and fornix fibers are injured in heart failure

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Abstract

Cognitive abnormalities, including memory deficits, are common in heart failure (HF). Brain structures, including the hippocampus, fornix, and thalamus participate in memory processing, and most show structural injury and functional deficits in HF. The mammillary bodies and fornix play essential roles in spatial and working memory processing, interact with other structures, and may also be injured in HF. We assessed mammillary body volumes and cross-sectional fornix areas in 17 HF and 50 control subjects using high-resolution T1-weighted magnetic resonance images. Mammillary body volumes and fornix cross-sectional areas were significantly reduced bilaterally in HF, and these differences remained after controlling age, gender, and intracranial volume. Mammillary body and fornix injury may contribute to the compromised spatial and working memory deficits in HF. Pathological processes eliciting the damage may include injury accompanying hypoxic/ischemic processes in pathologic HF perfusion and breathing, and thiamine deficiency accompanying diuretic use and nutritional malabsorption in the condition.

Keywords

Anterior thalamus; Magnetic resonance imaging; Hippocampus; Thiamine; Ischemia; Memory

INTRODUCTION

Heart failure (HF) patients show multiple neuropsychological deficits, including emotional and cognitive abnormalities, and especially spatial and short-term memory deficits (Almeida and Flicker, 2001; Callegari et al., 2002; Ferguson et al., 1992; Grubb et al., 2000; Jiang et al., 2007). The neuropsychological deficits in HF likely result from compromised integrity of brain structures mediating the neural functions. Brain regions with structural injury, including scattered infarcts, appear on routine magnetic resonance imaging (MRI) (Almeida et al., 2005; Schmidt et al., 1991), and sites of gray matter volume loss (Woo et al., 2003), together with metabolic alterations (Lee et al., 2001) occur in the syndrome and may contribute to neuropsychological deficiencies in the condition.

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The extent of memory and other cognitive deficits in HF are so severe that self-care and other quality-of life aspects are compromised significantly (Vogels et al., 2007). The available evidence, derived from voxel-based morphometry or T2-relaxometry procedures (Woo et al., 2008; Woo et al., 2003), indicates that injury appears within hippocampal and thalamic brain sites in HF that may contribute to the emotional and cognitive dysfunction in the condition, including memory processing (Lavenex et al., 2006; Ridley et al., 2004). Other structures, such as the fornix and mammillary bodies serve significant roles in memory and affective circuitry (Buckley et al., 2004; Paredes et al., 2000; Santin et al., 1999), but both traditional volumetric procedures and T2-relaxometry are inherently so low resolution that adequate assessment of small structures, such as the mammillary bodies is precluded. The bodies receive fibers from the hippocampus via the fornix, send efferents to the anterior and dorsal thalamus (Aggleton et al., 2005; Shibata, 1992), and are essential to route signals between brain areas integrating memory information. The consequences of injury to the anterior and dorsomedial thalamus, hippocampus, and mammillary bodies, or to interconnecting fibers are severe; such damage accompanies other conditions characterized by major anterograde and other memory deficits. One such condition, Wernicke-Korsakoff's syndrome, results from injury induced by toxicity from chronic alcohol consumption accompanied by loss of neuroprotection from thiamine deficiency (van Asselen et al., 2005). Alzheimer's disease also shows mammillary body and fornix injury and severe memory deficits (Copenhaver et al., 2006), and conditions associated with diuresis, anorexia, or intestinal malabsorption all present signs of anterograde memory loss (Harper, 2006). Mammillary body volumes are reduced in obstructive sleep apnea patients (Kumar et al., 2008), and these patients also exhibit compromised memory and cognitive functions (Bedard et al., 1991; Naegele et al., 1995).

The cognitive and memory deficits found in HF suggest the possibility that the mammillary bodies or afferent fibers have been injured in a similar fashion as found in other conditions with significant memory-deficiencies. The aim was to evaluate mammillary body volumes and fornix cross-sectional areas in HF and control subjects using high-resolution structural MRI and manual volume tracing procedures. We hypothesized that the mammillary bodies and fornix fibers in HF patients would show damage compared to control subjects.

MATERIALS AND METHODS

Subjects

Seventeen HF (mean age ± SD, 54.4 ± 8.1 years; range, 40–65 years; male, 12; LVEF, 0.28 ± 0.07, NYHA Class II, 16, III, 1) and 50 control subjects (age, 50.6 ± 7.0 years; range, 40–66 years; male, 29) were studied. Heart failure subjects were diagnosed based on national diagnostic criteria (Radford et al., 2005), and recruited from the Ahmanson-University of California at Los Angeles (UCLA) Cardiomyopathy Center and Los Angeles community. Four HF subjects had type II diabetes. The underlying HF etiology was ischemic in 5 subjects and idiopathic in 12 HF patients. None had evidence or history of alcohol-induced cardiomyopathy. All HF patients were treated with angiotensin receptor blockers or angiotension-converting enzyme inhibitors, beta blockers, and diuretics; body weight and medication doses were stabilized for at least six months before MRI studies. Control subjects were healthy, without clinical history of cardiovascular, stroke, respiratory, or neurological disorder, and recruited through greater Los Angeles area. Exclusion criteria for HF and control subjects were claustrophobia, non-removable metal such as braces, embolic coils, pacemakers/implantable cardioverter-defibrillators, and stents, and inability to lay supine, and body weight more than 125 kg (scanner limitation). Control and HF subjects provided written and informed consent prior to the study, and the study protocol was approved by the Institutional Review Board at UCLA.

Depressive and anxiety symptoms

Depressive symptoms were evaluated using the Beck Depression Inventory (BDI)-II (Beck et al., 1996), and anxious symptoms were evaluated by the Beck Anxiety Inventory (BAI) (Beck et al., 1988) in both HF and control subjects. Both instruments are self-report questionnaires, commonly used in medical condition, and were administered immediately before or after the MRI studies.

Magnetic resonance imaging

All brain studies were performed using a 3.0 Tesla MRI scanner (Magnetom Tim-Trio, Siemens, Erlangen, Germany), while subjects lay supine. Motion was minimized by using foam pads on both sides of the head. Two high-resolution T1-weighted image volumes, covering the entire brain, were collected using a magnetization prepared rapid acquisition gradient-echo sequence [repetition time (TR) = 2200 ms; echo-time (TE) = 2.2 ms; inversion time = 900 ms; flip angle (FA) = 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, 2 = 17, 134 ms; FA = 130°; matrix size = 256 × 256; FOV = 230 × 230 mm; slice thickness = 4.0 mm) were also collected simultaneously, using a dual-echo turbo spin-echo pulse sequence in the axial plane for visual assessment of any structural abnormalities.

Data analysis

High-resolution T1-weighted images were evaluated to ensure the absence of movement artifacts. T1-weighted images, and T2- and PD-weighted images of HF and control subjects were also visually evaluated for any gross pathology, such as infarcts, and for the presence of any mass lesions near the hypothalamus that might alter mammillary body or fornix morphology.

We used the statistical parametric mapping package SPM5 (Wellcome Department of Cognitive Neurology, UK; http://www.fil.ion.ucl.ac.uk/spm/), MRIcron (http://www.sph.sc.edu/comd/rorden/mricron/install.html), and Matlab-based (The MathWorks Inc, Natick, MA) custom software to process brain images.

Total intracranial volume calculation—High-resolution T1-weighted image volumes were averaged to increase signal-to-noise ratio, and images were reoriented (without warping) into a common space. The averaged and reoriented T1-weighted images were partitioned into gray matter, white matter, and CSF probability maps, using the unified segmentation (Ashburner and Friston, 2005) approach implemented in SPM5 [Gaussian per class ≥ (3, 2, 2, 5); bias full-width-at-half-maximum ≥ 70 mm cutoff; sampling distance ≥ 2]. Voxels with a probability value = 0.5 in gray, white, and CSF probability maps were calculated, and whole brain gray matter, white matter, and CSF volumes were derived by multiplying the counted voxels by the voxel volume. The total intracranial volume (TIV) was calculated by adding gray matter, white matter, and CSF volumes.

Mammillary body volume quantification—Brain areas containing the mammillary bodies were oversampled to a resolution of 0.2 × 0.2 × 0.2 mm, using averaged and reoriented T1-weighted images. Using MRIcron, a single investigator, unaware of subject group category, manually outlined body structures. Both bodies were differentiated from surrounding tissue parenchyma by their lighter gray color, and outlined after partitioning the midline from coronal and axial planes (Fig. 1A-I, II, crosshairs). Medial left or right mammillary body borders were outlined by tracing tissue in the sagittal plane of the midline (Fig. 1A-III). We determined the superior and inferior “mammillary notches” that indicated the superior and lateral boundaries of the body (Callen et al., 2001), using a central slice in the coronal view. Using the central coronal plane as a guideline, body outlines were traced; tracing continued through consecutive

sagittal slices, moving medially-laterally from the medial section. Disappearance of the bodies in the central coronal section defined the lateral boundaries. Mammillary body boundaries were smoothed, moving from anterior to posterior regions in the coronal plane. Axial views were also checked for boundary smoothness (Fig. 1A-IV). The same tracing procedure was used for the remaining body. We counted outlined voxels in both mammillary bodies, and body volumes for each side were derived by multiplying the number of voxels by the voxel volume.

Intra and inter subject reliabilities—Intra-subject reliability for mammillary body volume tracing was established by repeating the manual tracings and comparing mammillary body volumes in 8 randomly (5 controls, 3 HF) selected subjects by the original investigator. Another investigator also performed the manual tracing in the same subjects to evaluate inter-subject reliability. Intra-subject ($r = 0.96$, $p < 0.001$) and inter-subject ($r = 0.98$, $p < 0.001$) reliabilities were high for volume tracing.

Fornix cross-sectional area calculation—High-resolution averaged and reoriented T1-weighted images were oversampled ($0.2 \times 0.2 \times 0.2$ mm) in brain areas immediately dorsal to the septum containing the columns of the fornix. Using a coronal view, both left and right fornix fibers were marked before entering the septum parallel to the anterior commissure (Fig. 1B-I). The tags provided boundaries for the fibers in the medial-lateral direction. In a sagittal view, caudal-rostral borders were marked for both fornix columns (Fig. 1B-II). The coronal and sagittal boundaries provided borders for both columns (crosshairs in Fig.1B-III) in the axial view. Using axial views with the crosshairs, both left and right fornix cross-sectional areas were outlined separately (Fig. 1B-IV). Voxels from fornix cross-sectional views on each side were counted, and areas were calculated by multiplying the voxel count by the voxel area.

Statistical analysis

The Statistical Package for the Social Sciences (SPSS, V 15.0, Chicago, IL) was used for data analyses. Demographic and psychological variables of HF and control subjects were evaluated with Chi-square and independent t-tests. Between HF and control subjects, the mammillary body volume and cross-sectional fornix area differences were assessed with independent t-tests. We also performed a multivariate analysis of covariance (MANCOVA) to determine the mammillary body volume and fornix cross-sectional area differences between HF and control groups, with age, gender, and TIV included as covariates. All tests were two-tailed, and significance levels were established at $p < 0.05$.

Correlations between age, body mass index (BMI), BDI-II, BAI, and cross-sectional fornix areas with mammillary body volumes in HF and control subjects combined, and in HF subjects alone were assessed with Pearson's correlation procedures. Intra- and inter-subject reliabilities were also established by comparing traced mammillary body volumes with Pearson's correlation.

RESULTS

Demographic data and psychological measures from HF and control subjects are summarized in Table 1. Significant differences in BMI, BDI-II, and BAI appeared between control and HF subjects. However, no significant differences in age or gender emerged between groups.

Reduced mammillary body volumes and fornix cross-sectional areas in HF were visually apparent on high-resolution T1-weighted images from most individual HF subjects (Fig. 2, Fig. 3), and this impression was confirmed with statistical assessment. In control subjects, the average left mammillary body volume was 102.19 ± 18.45 mm^3, and the right mammillary body volume was 96.71 ± 18.19 mm^3 (Fig. 4A). The average left side body volume for HF subjects was 79.09 ± 17.28 mm^3, and the right side volume was 79.91 ± 19.30 mm^3 (Fig. 4A).

Both left and right mammillary body volumes differed significantly between the HF and control groups (independent t-test; left, $p < 0.001$; right, $p < 0.003$). Significant volume differences remained between control and HF groups when evaluated with MANCOVA, with age, gender, and TIV included as covariates (left, $p < 0.001$; right, $p < 0.01$).

The average left side fornix cross-sectional area in control subjects was 11.55 ± 2.02 mm^2, and the right cross-sectional area was 12.48 ± 2.25 mm^2 (Fig. 4B). In HF subjects, the average left side fornix cross-sectional area was 8.62 ± 1.76 mm^2, and for the right side was 8.55 ± 1.90 mm^2 (Fig. 4B). Both left and right fornix cross-sectional areas were significantly reduced in HF, compared to control subjects (independent t-test; left, $p < 0.001$; right, $p < 0.001$), and these differences remained after controlling for age, gender, and TIV (MANCOVA; left, $p < 0.001$; right, $p < 0.001$).

Mammillary body volumes showed no significant correlations with BMI, age, or BAI in combined HF and control subjects, or in HF subjects alone. However, a significant negative correlation appeared between mammillary body volumes and BDI-II scores in combined HF and control subjects (left, $r = -0.28$, $p < 0.025$; right, $r = -0.27$, $p < 0.031$). Mammillary body volumes also positively correlated with the corresponding fornix cross-sectional area (left, $r = 0.42$, $p < 0.001$; right, $r = 0.32$, $p < 0.009$) when HF and controls are combined.

DISCUSSION

Heart failure subjects showed reduced mammillary body volumes and cross-sectional areas of the fornix, compared to similar age- and gender- distributed control subjects. Mammillary body volumes correlated positively with fornix cross-sectional area for the corresponding side in combined HF and control groups. A substantial body of both animal and human evidence links both mammillary body and fornix damage to severe anterograde and spatial memory deficits (Buckley et al., 2004; Vann and Aggleton, 2004), suggesting that the memory issues in HF have a basis in structural injury.

The mammillary bodies with their fiber projections to other significant structures serve essential roles in learning and memory, including spatial and anterograde memory. The bodies are composed of medial and lateral nuclei, which receive fibers via the fornix from the hippocampus (Aggleton et al., 2005). Mammillary body or fornix damage results in navigation and spatial delayed-alternation task deficits in multiple species (Holmes et al., 1983; Irle and Markowitsch, 1982; Rosenstock et al., 1977; Vann and Aggleton, 2003; Whishaw and Maaswinkel, 1998). Spatial navigation is encoded with information from head-direction and angular velocity cells distributed in several brain sites, including the hippocampus (Leutgeb et al., 2000), anterior and dorsolateral thalamus (Blair and Sharp, 1995; Mizumori and Williams, 1993), postsubicular cortex (Taube, 1998), lateral mammillary body nuclei (Blair et al., 1998), and the dorsal tegmental nucleus of Gudden (Sharp et al., 2001). Medial mammillary body cells, which activate with the hippocampal theta rhythm, are associated with spatial memory performance (Bland et al., 1995; Kirk et al., 1996). Lateral mammillary body nuclei also participate in spatial working memory tasks, based on animal oxidative metabolic studies (Conejo et al., 2004); however, spatial navigation and learning appear to be principal functions. The imaging procedures used here were insufficient to partition lateral and medial portions of the mammillary bodies. Nevertheless, the substantial loss overall in the bodies suggests that both spatial learning and navigation would be impaired in HF patients.

Mammillary body and thalamic lesions also affect anterograde memory (Kapur et al., 1996; Langlais et al., 1992; Tanaka et al., 1997). Fornix injury elicits long term memory deficits, while mammillary body damage impairs episodic memory recall (Tsivilis et al., 2008). The hippocampus, its projecting fornix fibers to the mammillary bodies, and the mammillary

projections to the anterior thalamus are especially important for affective and cognitive regulation, including memory processing (Aggleton and Brown, 1999; Aggleton et al., 2005; Shibata, 1992). We earlier described functional impairment (Woo et al., 2005; Woo et al., 2007) and structural injury in HF (Woo et al., 2008; Woo et al., 2003) in most of these regions, including hippocampal, fornix, and thalamic areas; the limited resolution of the measurement techniques precluded adequate evaluation of the mammillary bodies. The collective findings suggest a system which regulates cognitive and affective behaviors, and processes memory, is damaged in HF, and may underlie several of the deficits found in the condition.

Significant negative correlations emerged between mammillary body volume and BDI-II scores. Classical brain structures that mediate mood regulation include the hippocampus, anterior cingulate and frontal cortices, and amygdala (Blumberg et al., 2003; Brooks et al., 2008; MacQueen et al., 2003; Rajkowska et al., 1999), and several of these structures show injury in HF. The mammillary bodies and fornix fibers are uniquely sited between hippocampal and thalamic areas to modify transmission for mood regulation. The mammillary bodies project to the anterior and dorsal thalamus, and the ventral anterior and dorsomedial thalamic nuclei interact with anterior cingulate and frontal cortices (Kaitz and Robertson, 1981; Vogt et al., 1987; Yeterian and Pandya, 1988); the latter structures have significant roles in depression (Brooks et al., 2008; Rajkowska et al., 1999). However, since the mammillary bodies are so closely integrated with hippocampal and other structures classically associated with depressive signs upon injury, it is unclear whether mammillary body damage or it's associated structures underlie the correlations with BDI scores.

The mechanisms underlying the fornix fiber injury and mammillary body volume loss here are unknown. The fornix fiber loss may stem from the hippocampal damage, found earlier in HF, with the fornix fiber loss resulting in mammillary cell injury (Loftus et al., 2000). Initial hippocampal damage may stem from significant alterations in cerebral perfusion found in HF, secondary to low cardiac output, with localized alterations in flow (Alves et al., 2005). In addition, HF subjects show a very high incidence of sleep-disordered breathing, with both obstructive sleep apnea and Cheyne-Stokes breathing appearing (Spaak et al., 2005). Impaired breathing leads to significant cerebral blood flow and blood pressure changes during apneic events, leading to potential ischemic or hypoxic exposure in brain sites. Central alterations in perfusion accompanying HF or apnea in the condition are more likely than cerebro-arteriosclerotic disease to cause the injuries, since we found no major tissue infarcts in the HF patients.

The hippocampus and thalamus both show significant injury in obstructive sleep apnea patients (Macey et al., 2002; Macey et al., 2008). Animal studies modeling sleep disordered breathing by intermittent hypoxia exposure during sleep show tissue injury in multiple areas, including limbic and cerebellar sites (Gozal et al., 2001; Pae et al., 2005; Veasey et al., 2004). Successive intermittent hypoxic periods trigger a variety of injurious processes, including oxidative and inflammatory sequences which can elicit neural injury (Ohga et al., 2003; Veasey et al., 2004; Zhan et al., 2005).

An additional possibility is that the mammillary bodies, being the recipient of long fibers of the fornix from the hippocampus, may be subjected to excitotoxic injury triggered by ischemic or hypoxic processes in a comparable fashion as cerebellar Purkinje cells are damaged by ischemia-induced excitotoxic injury with excessive activation of climbing fibers from the inferior olive (Pae et al., 2005; Welsh et al., 2002). Hyper-excited fornix fibers may injure mammillary body neurons following ischemia/hypoxia; excitotoxic injury has been suggested as a mode of injury in hippocampal neurons following excitation of projecting Schaeffer's collaterals during seizure discharge (Ang et al., 2006).

Mammillary body volume loss classically develops in conditions associated with thiamine deficiency, including Wernicke-Korsakoff's syndrome accompanying chronic alcoholism (van Asselen et al., 2005), cerebral beriberi (Kornreich et al., 2005), dialysis, and anorexia (Harper, 2006). Wernicke-Korsakoff's syndrome shows anterograde memory deficits, together with other neuropsychological inadequacies; the syndrome typically develops from alcohol toxicity, assisted by insufficient intake or absorption of thiamine. Thiamine plays significant roles in functioning of cells and neurons, and deficiency can introduce brain tissue changes through altered carbohydrate metabolism, which can lead to mitochondrial injury resulting in tissue necrosis, apoptosis (Singleton and Martin, 2001), and oxidative stress (Calingasan et al., 1999). In animal models, reduced thiamine levels elicit severe cognitive and spatial memory deficits which correlate with injury to multiple brain sites, including the mammillary bodies (Langlais and Savage, 1995). Early intervention with thiamine in Wernicke-Korsakoff's syndrome improves memory performance, but delayed treatment fails to reverse memory loss (Harding et al., 2000). The appearance of Korsakoff's-like symptoms in other circumstances in which thiamine deficiency appears, such as dialysis, anorexia, intestinal bypass or other malabsorption conditions provides clues to potential mechanisms operating in HF. Use of diuretics and malabsorption are common features of HF, and likely contribute to the markedly-reduced levels of thiamine found in this condition (da Cunha et al., 2002; Hanninen et al., 2006).

Thiamine deficiency also is prevalent in both Type I and Type II diabetes, with patients showing 76% reduced thiamine levels (Thornalley et al., 2007), likely resulting from frequent urination with loss of essential nutrition (Drivsholm et al., 2005). HF patients have a high incidence of diabetes, up to 48% in hospitalized HF patients (Deswal et al., 2004; Rathore et al., 2003); up to 22% of diabetic patients develop HF in older ages (Bertoni et al., 2004; Thrainsdottir et al., 2005). High glucose levels induce tissue injury (Vincent et al., 2002), and thiamine protects cells, axons, and the vasculature system against increased levels of glucose (Thornalley, 2005).

We speculate that processes accompanying alterations in cerebral perfusion and sleep-disordered breathing, operating without the neuroprotective benefit of adequate thiamine, damage hippocampal, thalamic, fornix and mammillary body structures and their projections in HF, and underlie a portion of the severe neurocognitive disturbances accompanying the condition. Interventions that target these etiologies for neurological damage (treatment of sleep-disordered breathing, stabilization/maintenance of cerebral perfusion, thiamine supplementation) may provide neuroprotection and/or alleviate neurocognitive abnormalities in HF.

Conclusions

Significantly reduced mammillary body volumes and fornix cross-sectional areas occur in HF patients over control subjects; both fornix fiber loss and diminished mammillary body volume likely contribute to anterograde and spatial memory deficits found in the syndrome. The mechanisms underlying the neuropathology are unknown, but may develop from reduced perfusion in the condition, assisted by compromised blood flow and hypoxia/ischemia accompanying sleep-disordered breathing that is common in HF. The frequent use of diuretics and the commonly-encountered nutritional malabsorption in HF may lead to nutritional deficiencies; thiamine, in particular, plays an essential neuroprotective role from excitotoxic and other processes injurious to neurons in other conditions associated with mammillary body damage.

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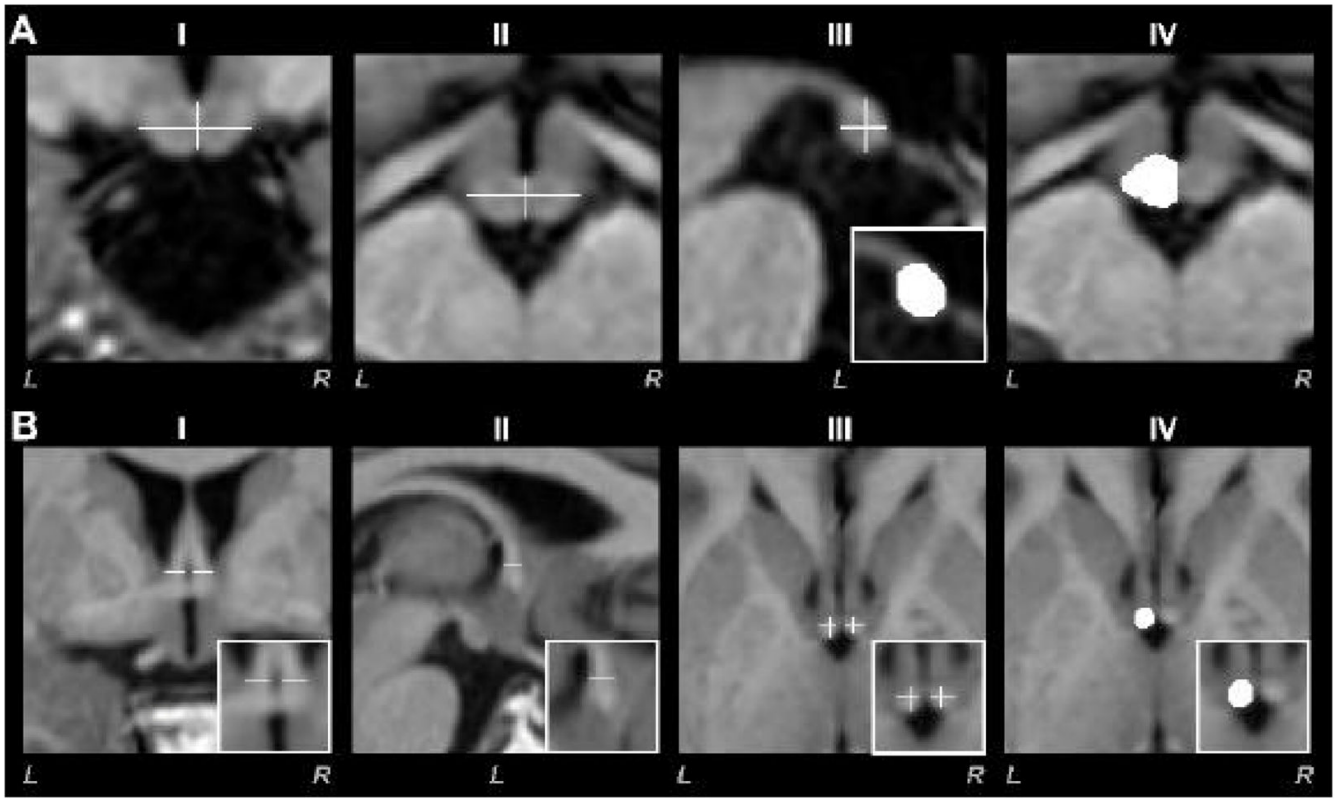

Fig. 1.

Brain images of different views show anatomical features used to calculate mammillary body volumes (A) and fornix cross-sectional areas (B). Midline borders for the left and right bodies were determined from coronal (A-I) and axial (A-II) views; vertical lines of the crosshairs used here indicate midline and medial borders, while extent to lateral borders are shown by horizontal lines in crosshairs. Caudal-rostral and dorsal-ventral extents were delineated using sagittal views (A-III; white crosshairs indicate mammillary body and corresponding outlined left body in white rectangle) after midline establishment, and coronal and axial views (A-IV) were used to assist determination of boundary edges. To assess fornix cross-sectional areas, coronal (B-I, white horizontal lines in magnified area within the white rectangle) and sagittal (B-II, white horizontal line in magnified area within the white rectangle) views were used to indicate fornix boundaries, providing crosshairs in axial views (B-III, white crosshairs within magnified area). The fornix cross-sectional area is outlined in axial view (B-IV, white structure within white rectangle). All images are in neurological convention (*L = Left, R = Right*).

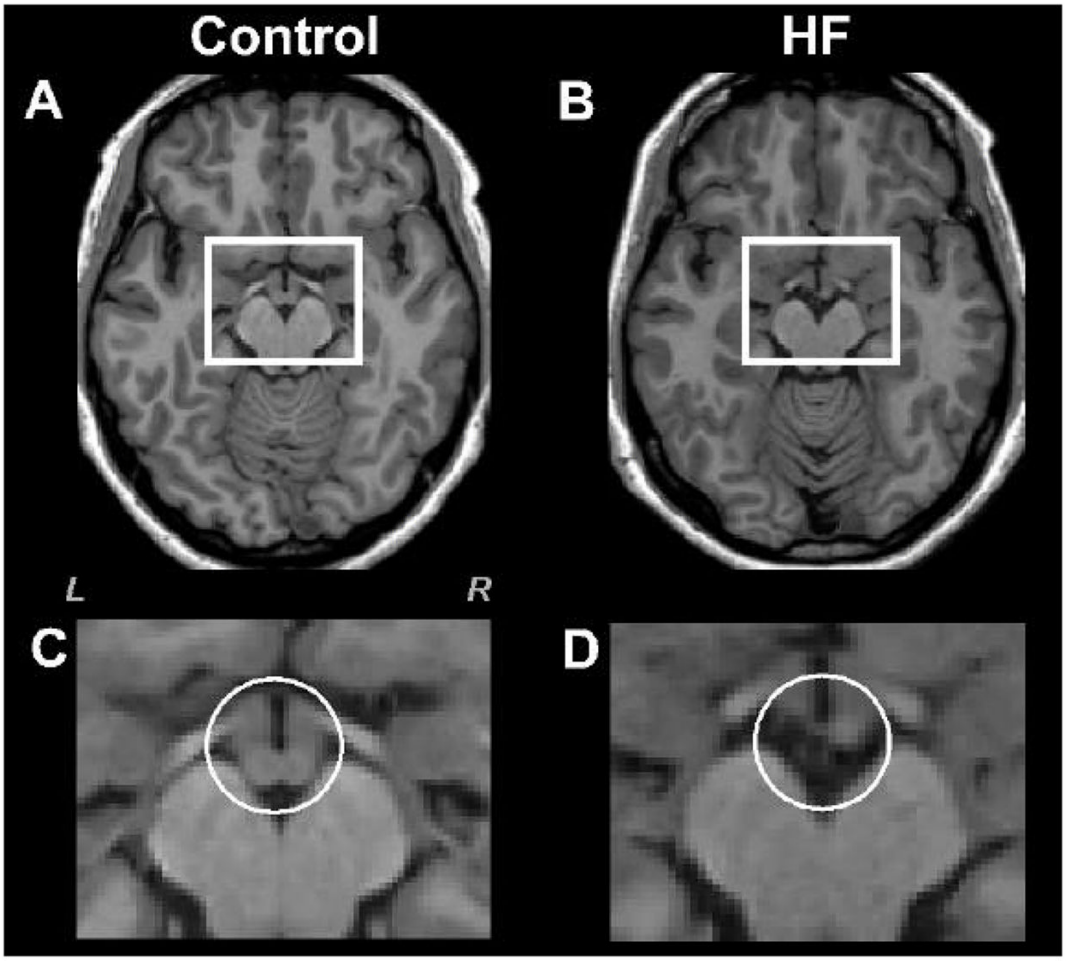

Fig. 2.

High-resolution T1-weighted images show mammillary bodies in a control (A) and HF (B) subject (white rectangles). All brain images are in neurological convention (*L* = *Left*, *R* = *Right*). Brain images (C) and (D) show magnified areas within the rectangles of the control (A) and HF subject (B). The right mammillary body in HF subject is smaller, and the left body is almost missing, compared to the control subject (C *vs* D, white circles).

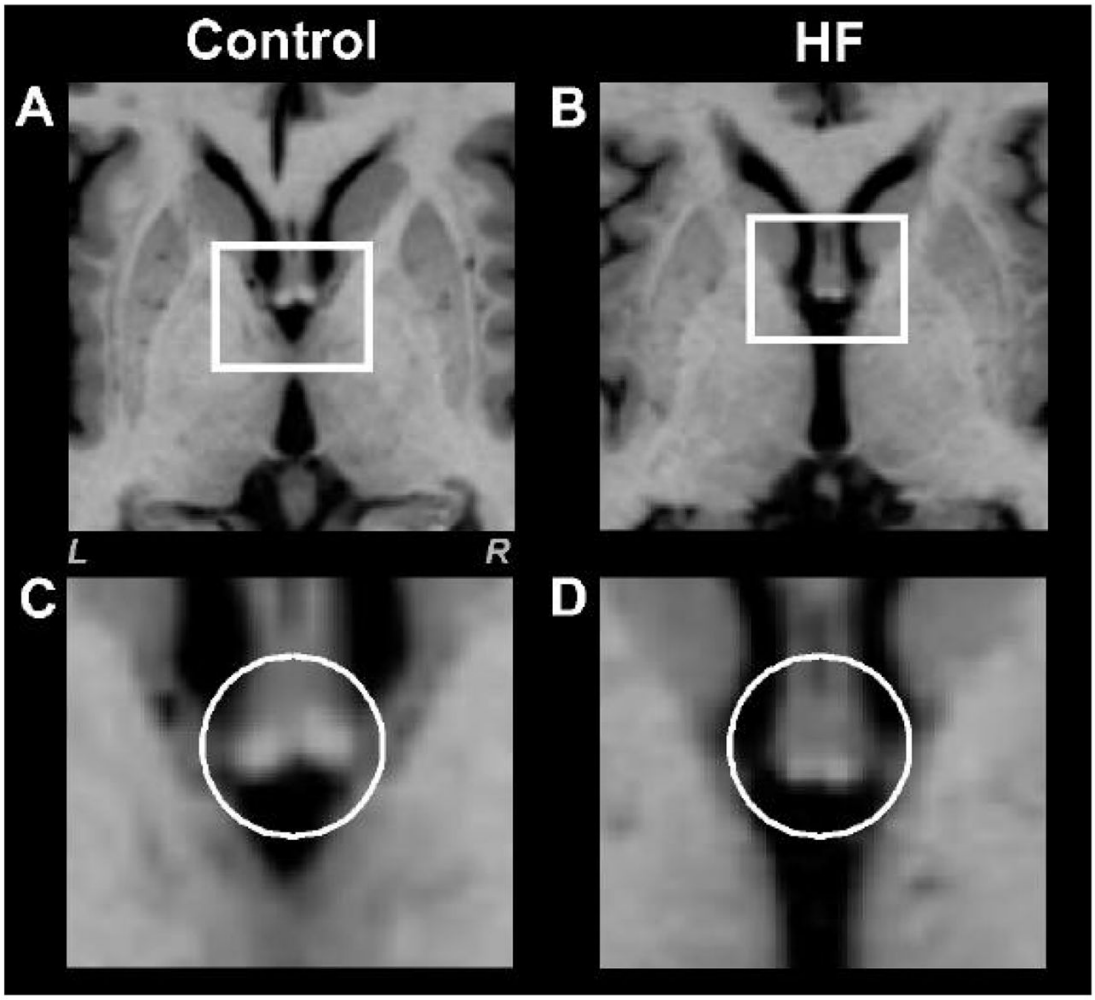

Fig. 3.

High-resolution T1-weighted oversampled images show fornix cross-sectional areas in a control (A) and HF (B) subject (white rectangles). Brain images (C) and (D) show magnified areas within the rectangles of the control (A) and HF subject (B). Both fornix areas are smaller in the HF than the control subject (C *vs* D, white circles). Figure conventions are the same as in Fig. 2.

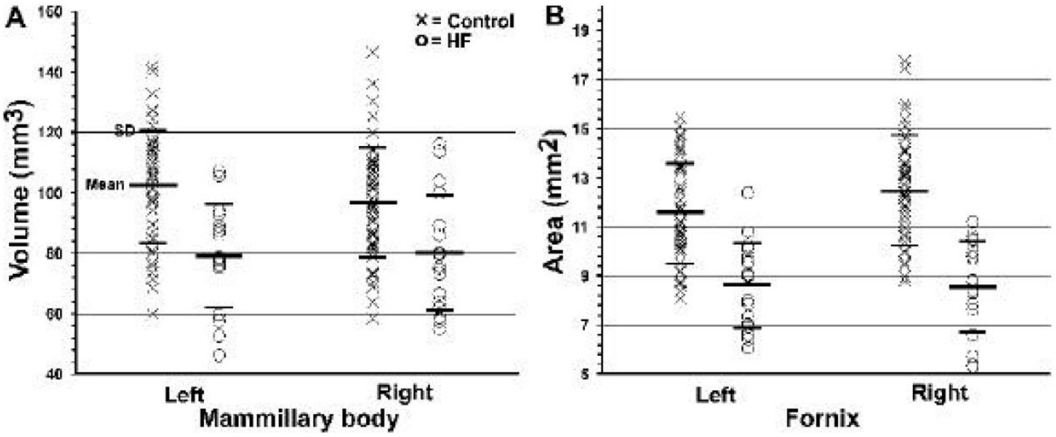

Fig. 4.

Scatter plot (A) shows individual mammillary body volumes and plot (B) shows fornix cross-sectional areas in control (×) and HF (O) subjects. Both left and right mammillary body volumes and fornix cross-sectional areas differed significantly between the groups.

Table 1

Demographics and characteristics of HF and control subjects

Demographics/Characteristics	HF (n = 17)	Controls (n = 50)	*p* value
Age (Mean ± SD, years)	54.4 ± 8.1	50.6 ± 7.0	0.07
Gender (Male: Female)	12: 5	29: 21	0.36
BMI (Mean ± SD, kg/m^2)	29.4 ± 5.7	24.9 ± 4.0	0.001
LVEF (Mean ± SD)	0.28 ± 0.07	–	–
BDI-II (Mean ± SD)	10.4 ± 7.6	4.3 ± 4.3	0.005[a]
BAI (Mean ± SD)	9.1 ± 7.1	4.4 ± 5.3	0.005

SD = Standard deviation; BMI = Body mass index; LVEF = Left ventricular ejection fraction; BDI-II = Beck Depression Inventory-II; BAI = Beck Anxiety Inventory;

[a] = Equal variance not assumed.