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Global and Regional Brain Mean Diffusivity Changes in Patients with Heart Failure

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Abstract

Heart failure (HF) patients show gray and white matter changes in multiple brain sites, including autonomic and motor coordination areas. It is unclear whether the changes represent acute or chronic tissue pathology, a distinction necessary for understanding pathological processes, and can be resolved with diffusion tensor imaging (DTI)-based mean diffusivity (MD) procedures. We collected four DTI series from 16 HF (age, 55.1±7.8 years; 12 male) and 26 controls (49.7±10.8 years; 17 male), using a 3.0-Tesla MRI scanner. MD maps were realigned, averaged, normalized, and smoothed. Global and regional MD values from autonomic and motor coordination sites were calculated using normalized MD maps and brain masks; group MD values and whole-brain smoothed MD maps were compared using analysis of covariance (covariates: age, gender). Global brain MD (HF vs. controls; Unit ×10⁻⁶ mm²/s; 1103.8±76.6 vs. 1035.9±69.4, p=0.038) and regional autonomic and motor site values (left insula, 1085.4±95.7 vs. 975.7±65.4, p=0.001; right insula, 1050.2±100.6 vs. 965.7±58.4, p=0.004; left hypothalamus, 1419.6±165.2 vs. 1234.9±136.3, p=0.002; right hypothalamus, 1446.5±178.8 vs. 1273.3±136.9, p=0.004; left cerebellar cortex, 889.1±81.9 vs. 796.6±46.8, p<0.001; right cerebellar cortex, 797.8±50.8 vs. 750.3±27.5, p=0.001; cerebellar deep nuclei, 1236.1±193.8 vs. 1071.7±107.1; p=0.002) were significantly higher in HF over controls, indicating chronic tissue changes. Whole-brain

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comparisons showed increased MD values in HF, including limbic, basal-ganglia, thalamic, solitary tract nucleus, frontal, and cerebellar regions. Brain injury occurs in autonomic and motor control areas, which may contribute to deficient functions in HF. The chronic tissue changes likely result from processes which develop over a prolonged time-period.

Keywords

Autonomic; Insula; Cerebellum; Chronic injury; Diffusion tensor imaging; Dyspnea

Introduction

Heart failure (HF) patients show gray matter and axonal deficits in multiple autonomic, motor, cognitive and emotional regulatory brain areas (Kumar et al. 2009; Kumar et al. 2011; Woo et al. 2009; Woo et al. 2003). The nature of brain structural deficits is unclear; specifically, it is unknown whether the pathology results from transient or catastrophic events in close temporal relationship to recognition of the damage, or whether the injury developed from processes requiring substantial time periods to emerge. Determining the developmental course of pathology in HF is essential for understanding the ongoing injurious processes, which would help guide intervention strategies for neural protection in the condition.

Non-invasive magnetic resonance imaging (MRI) procedures can differentiate whether structural changes result from acute or chronic processes (Ahlhelm et al. 2002; Matsumoto et al. 1995). Diffusion tensor imaging (DTI)-based mean diffusivity (MD) is a measure of average water diffusion within tissue, and can show changes in tissue integrity, an index which is affected by extra-/intra-cellular water content and tissue barriers, including cellular and axonal membranes and macromolecules (Basser and Pierpaoli 1996; Le Bihan et al. 2001). The procedures show differential values in various pathological stages, with decreased MD values appearing in acute conditions, and increased MD values materializing in chronic injury (Ahlhelm et al. 2002; Matsumoto et al. 1995). The MD procedures have been used in various pathological conditions to characterize tissue damage, and may provide insights into altered states of brain tissue in HF (Ahlhelm et al. 2002; Matsumoto et al. 1995).

Our aim was to examine global and regional brain tissue changes, using DTI-based MD procedures, in HF and control subjects to determine whether the structural changes result from acute or chronic processes. We hypothesized that, based on the severity and duration of autonomic changes exhibited by these patients, both global and regional brain MD values, including autonomic and motor regulatory sites, would be increased in HF compared to control subjects, reflecting chronic tissue changes in the condition.

Materials and Methods

Sixteen hemodynamically-optimized HF and 26 healthy control subjects were studied. Demographic, biophysical, and clinical variables of HF and control subjects are summarized in Table 1. All HF subjects were diagnosed based on national HF diagnostic criteria

(Radford et al. 2005), showed dilated cardiomyopathy and systolic dysfunction, classified as New York Heart Association Functional Class III-IV, but included only NYHA Functional Class II subjects after HF treatment at the time of MRI, and were recruited from the Ahmanson-UCLA Cardiomyopathy Center. HF subjects with NYHA III and IV were excluded due to logistic reasons, since HF subjects with such classifications cannot lay supine in the MRI scanner for a long period. We performed brain MRI on subjects within one year of HF diagnosis to minimize variability in measures from disease onset. All HF subjects were hemodynamically-optimized before MRI, and underwent similar treatment and care. Heart failure subjects had no previous history of stroke or carotid vascular disease, and were treated with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, diuretics, and beta blockers titrated to specific hemodynamic goals. All control subjects were recruited from the UCLA Medical Center and West Los Angeles area using flyers and postings. All control subjects were healthy, screened for head injury, history of cardiovascular, cerebrovascular, respiratory, or neurological disorders, and use of cardiac or psychotropic medications that might introduce brain changes. None of the controls included in this study were taking any such medications, and denied acute head injury, or any potential chronic injury (e.g., football or hockey injury). We interviewed control subjects for the presence of obstructive sleep apnea, and suspected subjects underwent an overnight sleep study. Neither HF or control subjects had metallic implants; all had body weights less than 125 kg, and had no conditions contraindicated for an MRI scanner environment. All HF and control subjects gave written informed consent before the study, and the study protocol was approved by the Institutional Review Board of the University of California at Los Angeles.

Magnetic Resonance Imaging

Brain imaging of HF and control subjects was performed using a 3.0-Tesla MRI scanner (Siemens, Magnetom Tim-Trio, Erlangen, Germany), with an 8-channel phased-array head coil. Foam pads were placed on both sides of the head to minimize head motion-related artifacts. High-resolution T1-weighted images were acquired using a magnetization prepared rapid acquisition gradient-echo (MPRAGE) pulse 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]. Proton-density (PD) and T2-weighted images were collected simultaneously in the axial plane, using a dual-echo turbo spin-echo pulse sequence (TR = 10,000 ms; TE₁, 2 = 17, 134 ms; FA = 130°; matrix size = 256×256; FOV = 230×230 mm; slice thickness = 4.0 mm). Diffusion tensor imaging was performed using single-shot echo-planar imaging with twice-refocused spin-echo pulse sequence (TR = 10,000 ms; TE = 87 ms; FA = 90°; band width = 1346 Hz/pixel; matrix size = 128×128; FOV = 230×230 mm; slice thickness = 2.0 mm, no interslice-gap, diffusion values = 0 and 700 s/mm²; diffusion gradient directions = 12; separate series = 4). The parallel imaging technique, generalized autocalibrating partially parallel acquisition, with an acceleration factor of two was used in high-resolution T1-weighted, PD- and T2-weighted, and diffusion tensor imaging data acquisition.

Data Processing and Analysis

We used the statistical parametric mapping package SPM8 (<http://www.fil.ion.ucl.ac.uk/spm/>), DTI-Studio (v3.0.1) (Jiang et al. 2006), MRICroN (Rorden et al. 2007), and MATLAB-based (<http://www.mathworks.com/>) custom software for evaluation of images, data processing, and analyses.

High-resolution T1-weighted, PD-, and T2-weighted images of HF and control subjects were evaluated for any visible brain pathology, including tumors, cysts, or any other mass lesions. We also examined diffusion and non-diffusion weighted images of HF and control subjects for imaging or head motion-related artifacts before MD quantification. Neither HF nor control subjects showed major visible brain tissue changes, head-motion, or other imaging artifacts.

Calculation of MD maps—The average background noise level from outside the brain tissue was derived using non-diffusion and diffusion-weighted images, and we used this noise threshold in all subjects to suppress noise outside the brain parenchyma during MD calculations. Using diffusion- ($b = 700 \text{ s/mm}^2$) and non-diffusion-weighted images ($b = 0 \text{ s/mm}^2$), diffusion tensors were calculated using DTI-Studio software (Jiang et al. 2006), and principal eigenvalues (λ_1 , λ_2 , and λ_3) were derived by diagonalizing the diffusion tensor matrices (Basser and Pierpaoli 1996; Basser and Pierpaoli 1998). Using principal eigenvalues, MD maps [$\text{MD} = (\lambda_1 + \lambda_2 + \lambda_3)/3$] were derived from each DTI series (Basser and Pierpaoli 1996; Le Bihan et al. 2001).

MD maps: Realignment, averaging, normalization, and smoothing—Four MD maps, derived from each separate DTI series, were realigned to remove any possible misalignment due to head motion, and averaged. Similarly, non-diffusion weighted images (b_0 images) from each DTI series were realigned and averaged.

The averaged MD maps of all HF and control subjects were normalized to Montreal Neurological Institute (MNI) common space. Based on *a priori*-defined distributions of gray, white, and cerebrospinal fluid tissue types (Ashburner and Friston 2005), the averaged non-diffusion weighted images were normalized to MNI space, and the resulting normalization parameters were applied to the corresponding subject's MD and tissue probability maps and non-diffusion weighted images. We used an isotropic Gaussian filter (10 mm kernel) to smooth the normalized MD maps. We also normalized high-resolution T1-weighted images of HF and control subjects to MNI space; these images were averaged to derive a whole-brain mean background image for structural identification.

Global brain mask—We averaged the normalized gray matter probability maps from all HF and control subjects. Similarly, the normalized white matter probability maps from HF and control subjects were averaged. We thresholded the averaged gray and white matter probability maps (white matter probability > 0.3 ; gray matter probability > 0.3), and combined both thresholded probability maps to create one global brain mask.

Calculation of global brain MD values—The normalized MD maps of HF and control subjects were masked, using a global brain mask, to remove non-brain regions. We used the

masked MD maps of individuals to derive mean global brain MD values using MATLAB-based custom software.

Region-of-interest analyses—Region-of-interest (ROI) analyses were performed to determine regional MD values, including the insular cortices, hypothalamus, and cerebellar cortices and deep nuclei from HF and control subjects. Regional brain masks were created based on significant whole-brain voxel-by-voxel differences between groups for those regions, and values were extracted using these regional brain masks and normalized MD maps of HF and control subjects.

Statistical Analysis

We used the IBM Statistical Package for the Social Sciences (IBM SPSS, v 22, Armonk, NY) software to examine demographic and biophysical variables, and global and regional brain mean MD values. We used independent samples t-tests and Chi-square to examine the demographic and biophysical variables.

The global and regional brain MD values were examined for significant differences between HF and control subjects using analysis of covariance (ANCOVA), with age and gender included as covariates. We considered a $p < 0.05$ value statistically significant for all statistical tests. Regional brain differences between male and female control subjects are well-described (Menzler et al. 2011; Westerhausen et al. 2011); the odd ratio of sex in both groups mandated factoring gender as another covariate in the statistical model.

The normalized and smoothed MD maps were compared voxel-by-voxel between HF and control subjects using ANCOVA, with age and gender included as covariates (SPM8, uncorrected threshold, $p < 0.005$; minimum extended cluster size, 5 voxels). We used an arbitrary extended cluster size (5 voxels) to avoid brain areas showing unreliable significant differences between groups (Kumar et al. 2011). We overlaid brain clusters with significant differences between groups onto background images for structural identification.

Results

Demographic, biophysical, and clinical variables

Demographic, biophysical, and clinical data of HF and control subjects are summarized in Table 1. Heart failure subjects did not differ significantly in age, gender, or body mass index from control subjects.

Global and Regional MD values

Global and regional brain MD values of HF and control subjects are tabulated in Table 2. Mean global brain MD values were significantly increased in HF compared to control subjects, and similarly, regional autonomic and motor regulatory sites showed higher MD values in HF over control subjects (Table 2).

Whole-brain MD changes

Multiple brain sites in HF showed significantly increased MD values over control subjects (Fig. 1), including the frontal white matter (Fig. 2a), external and internal capsules (Fig. 2b, i), ventral hippocampus (Fig. 2c), cerebellar cortices (Fig. 2d; Fig. 3d,e), parietal cortices (Fig. 2e), mid and posterior cingulate cortices (Fig. 2f, g), extending to corpus callosum (Fig. 2n, p; Fig. 3f, g), septum/bed nuclei (Fig. 2j), putamen (Fig. 2k), insular cortices (Fig. 2l), caudate nuclei (Fig. 2m), ventral white matter (Fig. 2o), anterior and posterior thalamus (Fig. 2q, r; Fig. 3j), and occipital gray and white matter (Fig. 2h, s). Other sites with increased MD values in HF over control subjects included the genu of cingulate (Fig. 3a), extending to hypothalamus (Fig. 3b), ventrolateral tegmental area (Fig. 3c), cerebellar vermis (Fig. 3e), raphe, extending to nucleus of the solitary tract (NTS) (Fig. 3h), inferior cerebellar peduncles (Fig. 3k), and cerebellar deep nuclei (Fig. 3i).

Discussion

Overview

Heart failure subjects show increased MD values relative to control subjects over the entire brain and in specific brain regions; increased MD values normally reflect chronic tissue changes. Regional tissue damage typically appeared in autonomic and motor control sites, including the insular cortices, hypothalamus, and cerebellar cortices and deep nuclei. Other brain regions with damage included the limbic, basal-ganglia, thalamic, NTS, and frontal areas. The injury in these brain sites emerged in our earlier studies either as structural tissue changes or functional deficits, and was determined by various structural and functional MRI procedures during autonomic challenges (Woo et al. 2009; Woo et al. 2003; Woo et al. 2005). The long-term brain changes may result from multiple pathological processes, but ischemia and hypoxia accompanying the condition likely contribute.

Acute and chronic tissue changes and MD values

Non-invasive DTI-based MD procedures can be used to examine global and regional brain tissue integrity. MD values can be altered by several factors, including tissue barriers (Le Bihan et al. 1991), water content, and extra-cellular/axonal space. Acute hypoxia or ischemia establishes a sequence of energy pump failure, altering sodium, potassium, and calcium ionic flow, leading to cytotoxic edema, with cytotoxic processes decreasing extra-cellular/axonal water and introducing neuronal and axonal swelling (Dirnagl et al. 1999; Hossmann 1971; O'Dell et al. 1994). Such changes lead to restricted water diffusion within tissue, resulting in reduced MD values (Ahlhelm et al. 2002; Matsumoto et al. 1995). However, chronic stages of hypoxia or ischemia result in degeneration of neurons and axons, which allow more extra-cellular/axonal water content and increased space, permitting water molecules to move faster within tissue, leading to increased regional MD values (Ahlhelm et al. 2002; Matsumoto et al. 1995).

Since HF subjects showed global and regional increased MD values, the processes found here likely result from chronic pathological mechanisms. Chronic tissue changes may require a variable period of time to develop, ranging from a week to years, depending upon

the extent of hypoxic/ischemic stress. The history of our subjects suggests that pathological processes were operating for several years.

Autonomic, respiratory, and motor regulatory sites and brain changes

Multiple autonomic and motor control sites, including the insular and cingulate cortices, hypothalamus, NTS, and cerebellar cortices, vermis, and deep nuclei showed increased MD values, indicating tissue injury in these areas in HF over control subjects. Left and right insular cortices have different autonomic control roles, along with other affective and pain regulatory functions. Both human and animal studies indicate that the right insula is primarily involved in sympathetic modulation, and the left insula in parasympathetic regulation (Cechetto and Saper 1987; Oppenheimer et al. 1992; Oppenheimer et al. 1996; Zhang et al. 1998); both insular cortices serve numerous other sensory integration roles (Cechetto and Chen 1990; Oppenheimer et al. 1992; Shipley 1982). Insular cortices receive visceral sensory input from, and project to the hypothalamus, participating significantly in autonomic regulation (Oppenheimer et al. 1996; Saper 1982). Other major contributors to autonomic regulation, the cingulate and ventral medial prefrontal cortices (Critchley et al. 2003; King et al. 1999), also project to the insular cortices, and the mid and posterior cingulate cortices showed injury here. HF subjects show both long-lasting increased sympathetic and altered parasympathetic tone (Woo et al. 2005), and the insular and cingulate cortices and hypothalamic chronic tissue injury found here likely contribute to those altered autonomic aspects in the syndrome, as shown by distorted functional MRI signal responses in HF subjects to autonomic challenges, including the Valsalva maneuver and cold pressor (Woo et al. 2005; Woo et al. 2007).

The NTS and raphe projections assist cardiovascular regulatory processes that include baroreceptor and chemoreceptor reflexes, failure of which results in essential features that characterize the pathology of HF (Kumar et al. 2011). The NTS serves such a critical role in coordination of blood pressure and chemoreception that any injury to that structure would severely disrupt autonomic regulation.

Extensive cerebellar injury emerged in HF subjects, and this injury was predominantly on the right side, and was prominent in the vermis. Cerebellar regions, including the cerebellar cortices and deep nuclei, typically are associated with motor regulation. However, the cerebellar cortices, and especially the vermis (Moruzzi 1950) also serve autonomic and chemoreceptor roles, as well as respiratory motor regulation (Holmes et al. 2002; Lutherer and Williams 1986). Cerebellar injury is typically accompanied by breathing disorders (Chokroverty et al. 1984; Waters et al. 1998); cerebellar structures activate immediately on resumption of breathing after apnea (Lutherer and Williams 1986), and induce compensatory actions to dampen extreme blood pressure changes (Lutherer et al. 1983). Both the cerebellar cortex and fastigial deep nuclei respond significantly to autonomic challenges in adult control subjects examined with functional MRI procedures (Woo et al. 2005; Woo et al. 2007); both responses are diminished and distorted in HF subjects (Woo et al. 2005; Woo et al. 2007).

Cerebellar Purkinje cells project to cerebellar deep nuclei, and these deep nuclei project to medullary sympathetic nervous system regulatory regions (Yates and Bronstein 2005).

Injury to the cerebellar cortices and deep nuclei is suspected of contributing to the impaired blood pressure control, and especially the incidence of orthostatic hypotension and poor recovery from provoked elevations in blood pressure frequently found in HF subjects (Lutherer et al. 1983). Since the cerebellar deep fastigial nuclei are sensitive to CO₂ (Xu et al. 2001), injury to those nuclei may alter chemosensitivity, enhancing the potential for appearance of Cheyne-Stokes breathing patterns, a condition resulting from altered chemosensitivity which is common in HF (Woo et al. 2003).

Cognitive, mood, dyspnea, and language control regions and brain injury

HF subjects show a variety of cognitive issues, including memory deficits (Woo et al. 2009; Zuccala et al. 2005). Brain regions that regulate cognitive, behavioral, and planning functions include the hippocampus, anterior thalamus, fornix, mammillary bodies, caudate nuclei, putamen, cerebellum, and frontal cortices; the majority of these areas showed tissue injury in HF. The hippocampus sends information to the mammillary bodies via the fornix (Aggleton et al. 2005), and mammillary bodies send efferent signals to the anterior thalamus and more caudal structures (Shibata 1992). Both the hippocampus and anterior thalamus showed injury here; the mammillary bodies and fornix fibers showed damage in an earlier study which evaluated injury based on high-resolution anatomical MRI procedures (Kumar et al. 2009). The caudate nuclei send and receive information to multiple brain sites, including thalamic and frontal regions, via the putamen (all these areas showed tissue injury here), and contribute to higher order cognitive and affective functions (Naismith et al. 2002). Lesion studies show that caudate and putamen damage can result in behavioral and learning deficits, and similarly, deficits can be reproduced from damage in the frontal sites (Ell et al. 2006; Naismith et al. 2002). Cerebellar regions send and receive information from rostral brain structures, and also serve cognitive and affective brain functions (Haines and Dietrichs 1984). Thus, damage found here in cognitive, behavioral, and planning regulatory regions in HF may contribute to symptoms found in the syndrome.

Other common characteristics of HF patients include a high incidence of depression and elevated signs of dyspnea (Jiang et al. 2007). A number of brain regions, including the insula, cingulate, hippocampus, ventral medial prefrontal cortex, and cerebellar areas are damaged in subjects with depression without heart failure, and most of these sites are also injured in HF subjects (Agid et al. 2003; Haines and Dietrichs 1984; Keedwell et al. 2005). Dyspnea, the perception of breathlessness, is common in HF, and appears to be regulated by the cingulate, insular and cerebellar areas (Banzett et al. 2000; Peiffer et al. 2001). Those sites are injured here, possibly contributing to dyspneic feelings and reduced feelings of pleasure, both commonly found in HF.

Both the mid and posterior corpus callosum showed tissue injury in HF subjects. Corpus callosum fibers connect the two hemispheres, and play significant roles in communication and integration of sensory and other information between cortical sites. Mid corpus callosum fibers connect to language areas, with injured fibers contributing to expressive aphasia (Friederici et al. 2007), whereas posterior portions of the corpus callosum connect to primary/secondary visual regions, with damage contributing to visual issues (Rudge and Warrington 1991), as frequently anecdotally reported in HF subjects. Agenesis of the corpus

callosum in humans without HF leads to difficulties in communication and language (Friederici et al. 2007), and lesions in the posterior corpus callosum introduce visual impairments (Rudge and Warrington 1991).

Potential pathological mechanisms

Although the precise pathological mechanisms that contribute to brain tissue changes to autonomic, respiratory, motor, mood, and cognitive control sites are unclear, several possibilities exist. HF subjects show compromised cerebral perfusion, resulting from low cardiac output, a primary characteristic of the condition, as well as hypoxic/ischemic processes which accompany sleep disordered breathing (HF subjects show both obstructive and central sleep apnea) (Harper et al. 2014). Both aspects may contribute to brain changes in the condition. However, these conditions should show generalized hypoxia/ischemia-induced brain changes, but HF subjects show region-specific and localized tissue damage.

Another process contributing to damage may be the occurrence of initial injury in autonomic control sites, including the NTS, insular cortices, and cerebellar areas, from stroke, maldevelopment, or infection. Initial injury to NTS and other autonomic control sites may compromise vascular activity, with impaired vascular responses leading to altered perfusion, introducing secondary injury in limbic and other rostral brain areas; damage in these latter areas is commonly found in HF and also described in the current study.

The increased global and regional MD values in HF would suggest a chronic, rather than acute process. Any of the hypoxic or ischemic pathological processes would require a period of time to develop, and HF is a slowly emerging condition, typically requiring several years to manifest symptoms. The slow emergence of characteristics offers the potential for intervention before more-extreme pathological characteristics emerge.

Limitations

Limitations of this study include inclusion of only HF subjects classified as NYHA functional Class II. We excluded HF subjects with NYHA III and IV, since HF subjects with those categories have difficulty in laying supine in the MRI machine for long periods; thus, our results should not be generalized to other NYHA Functional Classes. Other limitations of this study include insufficient power (small sample size) to examine differences among clinically relevant subgroups of HF patients, recruitment of all HF subjects from single referral center, and treatment of HF subjects with background guideline-directed medical therapies.

Conclusions

Mean diffusivity measures showed increased global and regional values in multiple brain areas in HF, compared to control subjects, indicating chronic tissue changes in those sites. These areas included autonomic and motor regulatory sites, including the insular cortices, hypothalamus, and cerebellar cortices and deep nuclei, and other brain regions, including the limbic, basal ganglia, thalamic, frontal, NTS, and occipital regions that control cognitive and mood functions. The pathological mechanisms contributing to chronic tissue changes in HF

may result from a combination of ischemic and hypoxic processes accompanying the syndrome.

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Mean diffusivity (HF > Controls)

Figure 1.

Brain regions with significantly increased MD values in HF ($n = 16$) over healthy control ($n = 26$) subjects (uncorrected threshold, $p = 0.005$) are shown in glass brain format, with projections across the 3D onto 2D axial, sagittal, and coronal views.

Figure 2.

Brain sites with significantly increased MD values in HF over controls. Significantly increased MD values in HF appeared in brain sites, including the frontal white matter (a), external and internal capsules (b, i), ventral hippocampus (c), cerebellar cortices (d), parietal cortices (e), mid and posterior cingulate cortices (f, g), occipital gray and white matter (h, s), septum/bed nuclei (j), putamen (k), insular cortices (l), caudate nuclei (m), posterior corpus callosum (n, p), ventral white matter (o), and anterior and posterior thalamus (q, r). All brain images are in neurological convention (*L* = *Left*, *R* = *Right*), and the color scale shows *t*-statistic values.

Figure 3.

Brain regions with increased MD values in HF, compared to control subjects. Brain sites with increased MD values in HF included the genu of cingulate (a), extending to hypothalamus (b), ventrolateral tegmental area (c), cerebellar vermis (e), cerebellar cortices (d), extending to deep nuclei (i), raphe, extending to nucleus of the solitary tract (h), and inferior cerebellar peduncles (k). Figure conventions are the same as in Figure 2.

Table 1

Demographic, biophysical, and clinical data from HF and control subjects.

Variables	HF (n = 16)	Controls (n = 26)	P values
Age (years)	55.1±7.8	49.7±10.8	0.07
Gender (male: female)	12: 4	17: 9	0.43
BMI (kg/m ²)	29.6±5.8	26.4±4.3	0.07
LVEF (%)	27.7±6.7	-	-
HF diagnosis	NYHA Functional Class II	-	-
Handedness	Right, 15; Left, 1	Right, 21; Left, 3; Both, 2	-
Ethnicity	White, 10; African American, 2; Hispanic, 1; Asian, 1; Other, 2	White, 18; Hispanic, 4; Asian, 4	-

HF, Heart failure; BMI, Body mass index; LVEF, Left ventricular ejection fraction; NYHA, New York heart association.

Table 2

Global and regional brain MD values (mean $\pm$ SD; unit, 10^{-6} mm²/s) of HF and control subjects.

Brain sites	HF (n = 16)	Controls (n = 26)	P values	**P values
Global brain	1103.8 $\pm$ 76.6	1036.0 $\pm$ 69.4	0.005	0.038
Left insula	1085.4 $\pm$ 95.7	975.7 $\pm$ 65.4	< 0.001	0.001
Right insula	1050.2 $\pm$ 100.6	965.8 $\pm$ 58.4	0.001	0.004
Left hypothalamus	1419.7 $\pm$ 165.2	1234.9 $\pm$ 136.3	< 0.001	0.002
Right hypothalamus	1446.5 $\pm$ 178.8	1273.3 $\pm$ 136.9	0.003*	0.004
Left cerebellar cortex	889.1 $\pm$ 81.9	796.6 $\pm$ 46.8	<0.001	< 0.001
Right cerebellar cortex	797.9 $\pm$ 50.8	750.4 $\pm$ 27.5	<0.001*	0.001
Cerebellar deep nuclei	1236.1 $\pm$ 193.8	1071.7 $\pm$ 107.7	0.005*	0.002

MD, Mean diffusivity; SD, Standard deviation; HF, Heart failure;

* = Equal variances not assumed;

** = p values based on analysis of covariance (covariates, age and gender).