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Brain Axonal and Myelin Evaluation in Heart Failure

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Abstract

Although gray matter injury appears in heart failure (HF) patients, the presence, extent, and nature of axonal injury impacting on cardiovascular regulation and other functions is unclear. We performed diffusion tensor imaging (3.0-Tesla magnetic resonance imaging scanner) in 16 HF and 26 control subjects, and assessed whole-brain water diffusion parallel (axial diffusivity; axonal status) and perpendicular (radial diffusivity; myelin changes) to fibers. Regions with increased axial diffusivity only, indicating impaired axonal integrity, emerged in cardiovascular, hedonic, and pain regulatory areas, including basal forebrain, hypothalamic and limbic projections through the medial forebrain bundle and raphe magnus projections to the medulla and cerebellum. Other fiber paths between sites implicated in cognition, including limbic, basal-ganglia, thalamic, internal capsule, and corpus callosum were also altered. Sites with increased radial diffusivity only, indicating myelin breakdown, appeared in the corpus callosum, cingulate, and temporal, parietal, occipital, and frontal regions. Both higher axial and radial diffusivity, indicating loss of tissue integrity, appeared in parietal and occipital lobes, limbic regions, insula, internal capsule, cerebellum, and dorsolateral medulla. Axons and myelin are altered in HF, likely resulting from ischemic/hypoxic processes acting chronically and sub-acutely, respectively. The alterations would contribute to the multiple autonomic and neuropsychological symptoms found in HF.

Keywords

Axial diffusivity; Radial diffusivity; Nucleus of the solitary tract; Cerebellar peduncles; Autonomic; Cognition

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Conflict of interest

Authors declare no conflicts of interest.

Introduction

Heart failure (HF) patients show brain injury in autonomic, cognitive, and emotional regulatory areas as demonstrated by magnetic resonance imaging (MRI) procedures that exhibit both localized tissue loss and increased free water content [1, 2]. The structural changes are associated with altered autonomic control, as revealed by distorted central functional MRI signal responses to Valsalva and cold pressor autonomic challenges [3, 4], and likely underlie in part the impaired capability of HF patients to appropriately manage cardiovascular challenges or pain, or to accommodate certain cognitive or affect conditions [5, 6].

The high incidence of autonomic deficits, impaired cerebral autoregulation [3, 4, 7], low cardiac output [8], and sleep-disordered breathing characteristics in HF [9] raise the possibility of widespread hypoxia/ischemia-induced central changes which would affect nerve fibers as well as gray matter, with white matter changes reflected in myelin damage or fiber loss either independently or in combination. Some fiber changes appear in HF subjects based on T2-relaxometry procedures [1]; however, T2-relaxometry indicates only generalized tissue damage, and is unable to differentiate types of axonal changes. The description of myelin changes and axonal abnormalities is an essential step in understanding the nature of central nervous system damage on HF pathology, and to develop more effective therapies and management strategies.

Diffusion tensor imaging (DTI) is a more sensitive technique to detect extent and type of tissue change than T2-relaxometry. DTI-based indices include axial diffusivity, which measures diffusion of water molecules parallel to axons and indicates axonal status, and radial diffusivity that assesses water diffusion perpendicular to the fibers and primarily shows myelin changes [10, 11]. Both indices offer greater sensitivity to subtle tissue changes and provide more pathological information (axonal vs. myelin injury) over other DTI measures [10–13].

The evaluation of the nature of axonal injury may help to reveal the source of aberrant characteristics in HF. Many of the autonomic and other affected functions in HF rely on interactions between multiple brain structures for appropriate action, and injury to axons between these central structures would compromise such functions. The specific aim of this study was to assess whole-brain axial and radial diffusivity using DTI procedures in HF patients to provide a more complete description of affected tissue.

Materials and Methods

Subjects

We studied 16 hemodynamically-optimized HF patients and 26 control subjects. Heart failure patients were diagnosed based on national HF criteria [14], recruited from the Ahmanson-UCLA Cardiomyopathy Center and the community, diagnosed with advanced dilated cardiomyopathy (left ventricular ejection fraction < 0.40) and systolic dysfunction, and classified as New York Heart Association Functional Class II. Five HF subjects had ischemic etiology and 11 were idiopathic. Four HF subjects had type II diabetes and none had signs or history of alcohol-induced cardiomyopathy, stroke, or carotid vascular disease. All HF subjects were treated with angiotension-converting enzyme inhibitors or angiotensin receptor blockers, diuretics, and beta-blockers, and body-weight and medication doses were stabilized for at least six months before MRI examination. Control subjects were healthy, with no medications, and no diagnosed history of cardiovascular, cerebrovascular, respiratory, or any other neurological disorder, and were recruited through the university

campus and local community. We excluded all HF and control subjects with claustrophobia or with other conditions not suitable for a high-magnetic field environment.

The study protocol was approved by the institutional review board, and all subjects gave written consent before the study. We removed all personal identifiable information of subjects after completion of data evaluation.

Magnetic Resonance Imaging

Brain images were collected using a 3.0-Tesla MRI scanner (Magnetom Tim-Trio; Siemens, Erlangen, Germany), with a receive-only 8-channel phased-array head coil and a whole-body transmitter coil. Head motion was reduced by using foam pads on either side of the head. We collected high-resolution T1-weighted images 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]. Proton-density (PD) and T2-weighted images (TR = 10,000 ms; TE_{1, 2} = 17, 134 ms; FA = 130°; matrix-size = 256×256; FOV = 230×230 mm; slice-thickness = 4.0 mm) were acquired simultaneously in the axial plane, using a dual-echo turbo spin-echo pulse sequence. Diffusion tensor imaging was performed using a 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, b = 0 and 700 s/mm², diffusion directions = 12). Four separate DTI series were collected with the same imaging parameters for subsequent averaging. We used the parallel imaging technique, generalized autocalibrating partially parallel acquisition, with an acceleration factor of two in all scans.

Data Processing

We used the statistical parametric mapping package SPM8 (<http://www.fil.ion.ucl.ac.uk/spm/>), DTI-Studio (v3.0.1) [15], and MATLAB-based (The MathWorks Inc., Natick, MA) custom software for data processing and analyses. The MRICroGL software was used to display axial and radial diffusivity changes in three dimensions (<http://www.cabiatl.com/mricrogl/>). High-resolution T1-weighted, PD- and T2-weighted images of HF and control subjects were visually examined for any serious brain pathology such as tumors, cysts, or any other major mass lesion, which may contaminate axial and radial diffusivity values. A researcher with long-term (>10 years) neuroimaging experience reviewed those images; any subject with suspected pathology was referred to a clinical neuro-radiologist for further evaluation. Using DTI-Studio software, which allows visualizing diffusion-weighted images from all diffusion gradient directions, along with b₀ images, non-diffusion and diffusion-weighted images were examined for head motion-related or other imaging artifacts before axial and radial diffusivity calculations. If any different orientation resulting from head-motion was noticed across the all diffusion-weighted and b₀ images, the subject was excluded from the analyses.

Calculation of axial and radial diffusivity indices—The average background noise level was determined with non-diffusion and diffusion-weighted images from non-brain regions, and was used to suppress background noise during axial and radial diffusivity calculations for all subjects. Diffusion (b = 700 s/mm²)-weighted images, collected from 12 diffusion directions, and non-diffusion (b = 0 s/mm²) images were used to calculate diffusion tensor matrices using DTI-Studio software. The diffusion tensor matrices were diagonalized, and principal eigenvalues (λ_1 , λ_2 , and λ_3) were calculated at each voxel [16]. Axial ($\lambda_{||} = \lambda_1$) and radial diffusivity [$\lambda_{\perp} = (\lambda_2 + \lambda_3)/2$] values were calculated at each voxel using principal eigenvalues [10, 11], with voxel intensities on the axial and radial diffusivity maps showing the corresponding diffusion values.

Realignment, averaging, normalization, and smoothing—Axial and radial diffusivity maps, calculated from each DTI series, were realigned to remove any potential misalignment resulting from head motion, and averaged. Similarly, non-diffusion weighted images were also realigned and averaged.

The averaged axial and radial diffusivity maps were normalized to Montreal Neurological Institute (MNI) space; averaged non-diffusion weighted images were normalized to MNI common space, based on a *priori*-defined distributions of gray, white, and cerebrospinal fluid tissue types [17]. These resulting normalization parameters were applied to axial and radial diffusivity maps. We smoothed the normalized axial and radial diffusivity maps (Gaussian filter, 10 mm). High-resolution T1-weighted images of a control subject were also normalized to MNI space and used for structural identification.

Statistical Analysis

Demographics—We used the Statistical Package for the Social Sciences (SPSS, V 18.0, Chicago, IL) software to evaluate demographic data. Demographic data were examined with independent samples t-tests, and Chi-square. Significance levels were set at $p < 0.05$ for the demographic data evaluation.

Axial and radial diffusivity changes—The normalized and smoothed axial and radial diffusivity maps were compared voxel-by-voxel between groups using analysis of covariance, with age and gender as covariates (SPM8, uncorrected, significance level set at $p < 0.005$; minimum extended cluster size, 5 voxels). The extended cluster size was arbitrary, and was used to avoid brain sites showing significant differences between groups with a cluster size less than 5 voxels, which may not represent actual changes. Clusters with significant differences between the groups on statistical parametric maps were partitioned into sites that showed axial diffusivity changes only, radial diffusivity changes only, and both axial and radial diffusivity changes. The clusters with significant group differences were overlaid onto normalized T1-weighted images for anatomical identification.

Results

Demographics

Demographic data of HF and control subjects are presented in Table 1. No significant differences in age, gender, or body mass index appeared between HF and control subjects.

Axial and radial diffusivity

Significantly increased axial and radial diffusivity, indicating severe changes to tissue, appeared in several brain areas in HF over control subjects, controlling for age and gender. No brain sites emerged with increased axial or radial diffusivity values in control subjects in comparison to HF.

Loss of axonal integrity, as indicated by axial diffusivity, emerged in major limbic, motor, and cardiovascular regulatory pathways involved in cardiovascular control, including fibers from the raphé magnus, extending to the nucleus of the solitary tract (NTS) (Fig. 1a), through the inferior cerebellar peduncles (Fig. 1f,h) to the cerebellar cortex and vermis (Fig. 1i,j). Major injury also emerged in medial forebrain fibers, extending from the genu of the cingulate cortex (Fig. 1c), projecting from the basal forebrain/preoptic area and the entire extent of the hypothalamus (Fig. 1d), and septum/bed-nucleus (Fig. 1k) to the ventral tegmental area (Fig. 1e,g). This fiber injury was joined by the mammillo-thalamic tract, from the mammillary bodies to the anterior thalamus (Fig. 1l; Fig. 2i), with affected fibers in the mammillo-tegmental tract (Fig. 2a). Other fiber injury in the memory circuitry of the

hippocampal-mammillary system emerged, with damage to the fornix (Fig. 2b), extending to the ventral cingulum bundle and hippocampus (Fig. 2c). The basal ganglia and surrounding white matter were also affected, including the superior occipito-frontal fasciculus (Fig. 2d) extending to the caudate nuclei (Fig. 2e) and nearby anterior insula (Fig. 2h), putamen (Fig. 2j), mid corpus callosum (Fig. 1b), anterior and posterior portions of the internal capsule (Fig. 2f,g,l), and medial-posterior thalamus (Fig. 2k), as were isolated areas of cerebellar simple lobule (Fig. 2m).

Fewer areas with myelin damage, indicated by increased radial diffusivity emerged; the areas included bilateral frontal (Fig. 3a,b) and parietal (Fig. 3e) white matter, mid and posterior cingulate cortices extending to the corpus callosum (Fig. 3c,f,h,i), left occipital white matter (Fig. 3j), right superior temporal white matter (Fig. 3k), and right posterior cingulum bundle (Fig. 3d).

Multiple brain regions showed both significantly higher axial and radial diffusivity, including bilateral parietal (Fig. 4a) and occipital lobes (Fig. 4c,d), bilateral anterior thalamus (Fig. 4e,f), left anterior and mid insula and anterior internal capsule (Fig. 4b,i), right posterior hippocampus, extending to cingulum bundle (Fig. 4h), left dorsolateral medulla (Fig. 4j), right cerebellar culmen and quadrangular lobule (Fig. 4k,l), left pyramid of the vermis (Fig. 4n) and inferior cerebellar peduncle (Fig. 4g), and caudal cerebellar cortex (Fig. 4m).

Discussion

Overview

HF patients show significant brain injury, as indicated by a range of structural and functional MRI procedures, in autonomic, cognitive, and emotional regulatory areas. Here, damage to white matter is outlined in more detail, with differentiation of axonal vs myelin changes. The axonal changes are of particular concern for the HF condition, since major axonal pathways between essential structures regulating cardiovascular functioning, pain regulation, and hedonic and other affective aspects were affected. These pathways include projections from the caudal raphe to the NTS and to the cerebellum, as well as the medial forebrain bundle, a major pathway carrying signals from limbic autonomic regulatory areas in the cingulate, septum, basal forebrain, and amygdala through the hypothalamus to the midbrain ventral tegmental area. In addition to involvement of autonomic structures, the medial forebrain bundle connected to affected fibers from the damaged hippocampus and fornix to the mammillary bodies, and from the mammillary bodies to the anterior thalamus and to the tegmentum. The hippocampal/fornix/mammillary body/anterior thalamus system plays a critical role in memory processing. Other cognitive/affective areas were affected, with altered tissue appearing in the caudate and insular cortex, internal capsule, and medial thalamus. Indications of myelin breakdown appeared in fewer areas, but were prominent in the posterior cingulum bundle and temporal, parietal, occipital, and frontal areas. Other brain sites showed both increased axial and radial diffusivity, suggesting a combination of myelin and loss of axonal integrity, in the internal capsule, cerebellar sites, and dorsolateral medulla. Many of these sites had showed structural injury earlier, based on T2-relaxometry procedures [1], and those areas overlapped regions of functional deficits during autonomic challenges [3, 4]. The findings here would suggest a major impact on cognitive, affective, autonomic and physiologic activity in HF, and should contribute to these impaired functions in the condition.

Axial and Radial Diffusivity Changes

Multiple brain regions in HF appeared either with increased axial diffusivity or radial diffusivity, or with both increased axial and radial diffusivity. Axial diffusivity measures motion of water molecules parallel to the tissue fibers, and alterations in axial diffusion primarily indicate axonal status [10, 11]. Increased axial diffusivity can result from reduced axonal-density or caliber that allows axons to straighten due to increased intra-axonal space, and thus, increases axial diffusivity [18]. The majority of HF subjects experience hypoxic conditions resulting from sleep-disordered breathing [9, 19], and ischemic events from low cardiac output [8], and such mechanisms may introduce fiber injury, including reduced axonal density or caliber, or a combination of both as the disease progresses.

Radial diffusivity measures diffusion of water perpendicular to the fibers, and principally indicates myelin status [10, 11]. Radial diffusivity increases with reduced myelin (a thinner myelin sheath allows water to penetrate faster), which can result from a range of pathological processes, including hypoxic/ischemic episodes or developmental issues; developmental pathology is not likely the case here with middle-aged subjects. Axon-supporting cells, oligodendrocytes that contribute to myelin formation, are extremely susceptible to hypoxia and high CO₂, conditions accompanying HF, and can contribute to the myelin injury reflected as increased radial diffusivity [20]. Animal models of demyelination show increased radial diffusivity, with equivalent axial diffusivity values as controls in sub-acute conditions [10]. Other demyelinating conditions, such as exposure to particular drugs, also show increased radial diffusivity in a densely-packed structure, the corpus callosum, without significant alterations in axial diffusivity [21]. Since increased radial diffusivity appears initially, before increased axial diffusivity develops in ischemic conditions [22], brain regions that show only increased radial diffusivity likely represent acute changes resulting from hypoxic/ischemic processes.

Both increased axial and radial diffusivity can indicate brain areas with loss of structural integrity, with a combination of axonal and myelin injury. Patients with multiple sclerosis and other neurodegenerative conditions which are accompanied by demyelination along with axonal loss, show both increased axial and radial diffusivity in white matter areas [23]. HF patients are subjected to ischemic/hypoxic processes that may contribute to such pathology, which may result in a combination of axonal and myelin injury in chronic conditions, reflected as both increased axial and radial diffusivity measures.

Potential Factors Contributing to Tissue Injury and Specificity of Damage

Several factors can contribute to or exaggerate brain tissue injury induced by hypoxic/ischemic processes in HF. Gray matter changes in the basal forebrain, septum and other sites, which may contribute to alterations in fibers of the medial forebrain bundle shown here, appear in animal (both murine and rat) intermittent hypoxia studies designed to mimic obstructive sleep apnea [24, 25]. Both obstructive sleep apnea and Cheyne-Stokes apnea are breathing pattern abnormalities commonly reported in HF subjects and result in intermittent periods of O₂ desaturation. A majority of HF patients also show impaired cerebral autoregulation [26], which can impose a greater ischemic burden, leading to severe tissue injury.

Hypoxia combined with inadequate levels of thiamine is more injurious to cells than hypoxia with normal thiamine levels [27]. Thiamine, along with magnesium, is an essential component for carbohydrate metabolism, and plays a critical role in function of cells and neurons, particularly in conditions which lead to excitotoxic injury associated with high metabolic demands on neurons. Thiamine deficiencies can lead to mitochondrial injury with tissue necrosis, oxidative stress [28], and apoptosis [29]. Reduced thiamine levels are

common in HF [30, 31], likely resulting from use of diuretics and malabsorption in the condition. Hypoxic/ischemic processes, together with inadequate thiamine levels, crucial for neuroprotection, may exaggerate brain tissue injury found in the condition.

Axonal injury was more prominent in a majority of brain areas in HF patients over myelin injury; few regions showed both increased axial and radial diffusivity. The specificity of such damage is unclear, but may represent stages in the progression of the disease, localized alterations in cerebral autoregulation, or differential protection from micronutrients in the presence of hypoxia/ischemia.

Autonomic and Pain Regulatory Fibers and HF

HF subjects show multiple autonomic, pain, and thermoregulatory and sleep-related abnormalities [7, 9, 19, 32]. Several brain regions, which have major regulatory roles for autonomic and physiologic functions, showed injury here in HF. These sites included the anterior insula, hypothalamus, including fibers of the medial forebrain bundle and preoptic regions, bed-nucleus, NTS, hippocampus, and cerebellar regions; most of these structures show abnormal functional MRI signal responses to autonomic and cardiovascular challenges in HF [3, 4]. The insular cortices are implicated in sympathetic and parasympathetic control [33], regulate baroreflex action [34], and modify hypothalamic activity [35], which is essential for regulating neuro-hormones, and body temperature [36]. Other structures, including the hippocampus and bed-nucleus, have also been implicated in hypothalamic-pituitary-adrenal axis activity [37], and contribute significantly to autonomic regulation. The raphe magnus is implicated in pain regulation, and the NTS and cerebellar projections serve essential cardiovascular control processes, including the baroreflex and chemoreflexes [38, 39]; deficiencies in those systems likely contribute substantially to pain perception and cardiovascular control deficits in HF. The findings here are supported by findings of bilateral lesions in the NTS in neuropathology studies of acute HF subjects [40]. The NTS findings reported here overlapped these previously-reported sites. The cerebellar cortex and deep nuclei, severely affected here, play major roles in regulation of blood pressure changes during body movement [41, 42], and in limiting extremes of hypo- and hypertension, with cerebellar damage likely compromising that regulation.

Cognitive and Depression Regulatory Fibers and HF

A majority of HF patients show cognitive deficits, including impaired attention, confusion, problems in complex planning, and in short-term memory [5, 43]. Brain sites that are involved in cognitive, behavioral, and planning functions, include the caudate nuclei, putamen, anterior thalamus, fornix, hippocampus, cerebellum, and frontal cortices; all areas showed fiber injury here in HF. The hippocampus sends projections to the mammillary bodies through the fornix [44], regions found damaged earlier, based on high-resolution structural data [45]. The mammillary bodies send efferent signals to the anterior thalamus for memory processing via the mammillo-thalamic tract [46], and showed injury throughout its entire course here. The caudate structures interact with several brain regions, including thalamic and frontal sites (dorsolateral prefrontal and lateral orbitofrontal cortices) through the putamen, and play a major role in mediation of higher cognitive and limbic functions [47]. Behavioral and learning abnormalities can be produced with caudate and putamen injury [47, 48], and those deficits can be reproduced with injury in frontal cortex regions [47]. Cerebellar sites send and receive projections from rostral brain regions, including the mammillary bodies [49], and are involved in higher cognitive and affective functions [50]. Injury found in these cognitive, behavioral, and planning regulatory areas may contribute to deficits in functions found in the syndrome.

HF patients show a very high incidence of depression, in which feelings of pleasure are greatly reduced. Descending fibers of the medial forebrain bundle [51] and hippocampus have significant roles in mediating hedonic behavior, and the axonal changes here may contribute to these aspects.

Limitations

All HF subjects used medications, which may protect or modify effects of perfusion or hypoxia on brain tissue. However, our HF group was homogenous in use of medications, *i.e.*, each subject used similar medications. The imaging procedures provided only limited spatial resolution, which restricted identification of smaller nuclei, including the NTS with its many neighboring structures. The normalization of axial and radial diffusivity maps may have exacerbated the already-limited spatial resolution, and thus, these findings are only valid within a few millimeters distance.

Clinical Significance

Since HF patients show widespread fiber injury between cognitive and autonomic regulatory sites, the deficits will likely interfere with routine life activities. The findings of major axonal deficits emphasize the need to better identify the pathophysiologic mechanisms in HF which may be contributing to these structural changes. It is also important to develop more effective therapies and management strategies in HF targeted to prevent axonal injury, such as providing interventions for sleep-disordered breathing, more aggressive evaluation and supervision of diabetes and thiamine status, evaluation of therapies to improve cerebral autoregulation, and to enhance cardiac output.

Conclusions

Axial and radial diffusivity measures show significant axonal and myelin alterations in HF, with reduced axonal density or caliber, or myelin, or both appearing in vital autonomic, analgesia, affective, and cognitive pathways, including the medial forebrain bundle and associated fibers from rostral limbic sites to the midbrain, an essential projection from the raphe nuclei to the medulla and cerebellum, and multiple fiber bundles in the cortex and limbic areas mediating cognitive and memory aspects. Brain axonal injury accompanies HF, perhaps due to accompanying ischemic or hypoxic processes, and can exacerbate the disease characteristics.

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Fig. 1.

3D and 2D views of brain sites showing significantly increased axial diffusivity, with no significant increase in radial diffusivity in HF over control subjects. Affected sites included the raphé magnus, extending to the NTS (a) and laterally and caudally to inferior cerebellar peduncles (f, h), and cerebellar vermis and cortical areas (i, j). Medial forebrain bundle fibers, extending from the genu of the cingulate (c), and passing from the basal forebrain and hypothalamus (d), and septum/bed-nucleus (k) to the ventral tegmental area (e, g), as well as the mammillo-thalamic tract, fibers from the mammillary bodies to the anterior thalamus (l), and mid corpus callosum (b) are affected. The color-bar shows t-statistic values for areas showing a significance level of $p < 0.005$, with a minimum of 5 extended voxels (uncorrected threshold, $t = 2.71$).

Fig. 2. 3D views of brain images showing sites with significantly increased axial diffusivity only in HF over control subjects. These regions included fornix fibers (b), ventral cingulum bundle and hippocampus (c), superior occipito-frontal fasciculus (d) extending to the caudate nuclei (e), anterior insula (h), putamen (j), anterior and posterior internal capsule (f, g, l), medial-posterior thalamus (k), and cerebellar simple lobule (m). Figure conventions are the same as in Fig. 1.

Fig. 3.

3D views of brain sites showing significantly increased radial diffusivity only, with no significant change in axial diffusivity, in HF over control subjects. Regions with myelin changes included frontal (a, b) and parietal (e) white matter, mid and posterior cingulate cortices, extending to the corpus callosum (c, f, h, i), left occipital white matter (j), and right superior temporal white matter (k) and posterior cingulum bundle (d). Figure conventions are the same as in Fig. 1.

Fig. 4.

3D and 2D views of brain areas showing both increased axial and radial diffusivity in HF over control subjects; brain clusters showing increased axial diffusivity values are overlaid onto background images for display. Similar regions also show significantly increased radial diffusivity, although with variable regional significance levels. Brain regions showing both increased axial and radial diffusivity included the bilateral parietal (a) and occipital areas (c, d), bilateral anterior thalamus (e, f), left anterior and mid insula and anterior internal capsule (b, i), right posterior hippocampus and cingulum bundle (h), left dorsolateral medulla (j), right cerebellar culmen and quadrangular lobule (k, l), left pyramid of the vermis (n) and

inferior cerebellar peduncle (g), and caudal cerebellar cortex (m). Figure conventions are the same as in Fig. 1.

Table 1

Variables	Heart failure (n = 16) [A]	Controls (n = 26) [B]	p values [A] vs [B]
Age (mean±SD, years)	55.1±7.8	49.7±10.8	0.07*
Gender (Male:Female)	12:4	17:9	0.51
BMI (mean±SD, kg/mm ²)	29.6±5.8	26.4±4.3	0.07*
LVEF (mean±SD, %)	27.7±6.7	-	-

* Equal variances not assumed; SD = Standard deviation; BMI = Body-mass-index; LVEF = Left ventricular ejection fraction.