



Brain Damage With Heart Failure

Cardiac Biomarker Alterations and Gray Matter Decline

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RATIONALE: Heart failure (HF) following heart damage leads to a decreased blood flow due to a reduced pump efficiency of the heart muscle. A consequence can be insufficient oxygen supply to the organism including the brain. While HF clearly shows neurological symptoms, such as fatigue, nausea, and dizziness, the implications for brain structure are not well understood. Few studies show regional gray matter decrease related to HF; however, the underlying mechanisms leading to the observed brain changes remain unclear.

OBJECTIVE: To study the relationship between impaired heart function, hampered blood circulation, and structural brain change in a case-control study.

METHODS AND RESULTS: Within a group of 80 patients of the Leipzig Heart Center, we investigated a potential correlation between HF biomarkers and the brain's gray matter density (GMD) obtained by magnetic resonance imaging. We observed a significant positive correlation between cardiac ejection fraction and GMD across the whole frontal and parietal medial cortex reflecting the consequence of HF onto the brain's gray matter. Moreover, we also obtained a relationship between GMD and the NT-proBNP (N-terminal prohormone of brain natriuretic peptide)—a biomarker that is used for screening, diagnosis, and prognosis of HF. Here, we found a significant negative correlation between NT-proBNP and GMD in the medial and posterior cingulate cortex but also in precuneus and hippocampus, which are key regions implicated in structural brain changes in dementia.

CONCLUSIONS: We obtained significant correlations between brain structure and markers of heart failure including ejection fraction and NT-proBNP. A diminished GMD was found with decreased ejection fraction and increased NT-proBNP in wide brain regions including the whole frontomedian cortex as well as hippocampus and precuneus. Our observations might reflect structural brain damage in areas that are related to cognition; however, whether these structural changes facilitate the development of cognitive alterations has to be proven by further longitudinal studies.

VISUAL OVERVIEW: An online [visual overview](#) is available for this article.

Key Words: brain imaging ■ coronary artery disease ■ gray matter ■ heart failure ■ magnetic resonance imaging

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Heat failure (HF) is a common condition, where heart injury leads to reduced pump efficiency of the heart muscle and decreased general blood flow. A common consequence can be insufficient oxygen supply to the entire organism, including the brain. While HF clearly shows neurological symptoms, such as fatigue, nausea, and

dizziness, long-term consequences for brain integrity are not well understood. It is well known from epidemiological studies that cardiovascular insults, including HF, increase the risk for later emergence of neurological diseases in late life, such as vascular dementia and Alzheimer disease.^{1,2} To shed light on the mediators of this association, several

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Novelty and Significance

What Is Known?

- Heart failure (HF) following heart damage leads to reduced pump efficiency. Subsequent decreased blood flow could cause insufficient oxygen supply to the brain.
- The effects of HF on brain structure are not well understood.
- Few studies have investigated regional gray matter decrease and its relation to HF.

What New Information Does This Article Contribute?

- Our case-control study disentangles the relationship between impaired heart function and structural brain change by correlating HF biomarkers and the brain's gray matter density (GMD) obtained by magnetic resonance imaging.
- Cardiac ejection fraction correlated positively, whereas NT-proBNP (N-terminal prohormone of brain natriuretic peptide) correlated negatively with GMD across frontal and parietal brain regions indicating detrimental effects of HF onto brain's gray matter.
- These data suggest a link between the brain's structure and function in patients suffering from HF.

HF following heart damage leads to reduced pump efficiency and insufficient oxygen supply to the brain. Effects of HF on brain structure are not well understood. In our case-control study, we investigated the relationship between impaired heart function and structural brain changes. We correlated HF biomarkers and the brain's GMD assessed by magnetic resonance imaging. Cardiac ejection fraction correlated positively with GMD across the whole frontal and parietal medial cortex indicating detrimental effects of HF onto the brain's gray matter. NT-proBNP—a biomarker for screening, diagnosis, and prognosis of HF—correlated negatively with GMD in the medial and posterior cingulate cortex as well as in the precuneus and hippocampus. Our study shows associations between brain structure and the HF biomarkers ejection fraction and NT-proBNP in wide brain regions including the frontomedian cortex as well as hippocampus and precuneus, brain areas related to cognition and affected in dementia. Our results suggest that the brain's structure and function are associated with cardiac function in patients suffering from HF.

Nonstandard Abbreviations and Acronyms

CAD	coronary artery disease
CIMT	carotid intima media thickness
CK	creatinine kinase
CK-MB	isoenzyme muscle brain of creatine kinase
EF	ejection fraction
EF1	ejection fraction, initial measurement
EF2	ejection fraction, follow-up measurement
GM	gray matter
GMD	gray matter density
HF	heart failure
LIFE	Leipzig Research Centre for Civilization Diseases
MR	magnetic resonance
MRI	magnetic resonance imaging
NAD	no abnormality detected
NT-proBNP	N-terminal prohormone of brain natriuretic peptide
NT-proBNP1	N-terminal prohormone of brain natriuretic peptide, initial measurement
NT-proBNP2	N-terminal prohormone of brain natriuretic peptide, follow-up measurement

SPM	statistical parametric mapping
TFCE	threshold-free cluster enhancement
VBM	voxel-based morphometry

studies have focused on the study of brain gray matter (GM) changes consequent to cardiovascular impairment. For example, Horstmann et al³ reported significant and widespread GM tissue loss in the entire cingulate cortex, precuneus, insulae, thalamus, and hippocampus, as well as neuropsychological impairment, in patients after cardiac arrest. Similarly, HF has been found to be associated with GM structural changes. Previous studies showed brain GM abnormalities comparing patients with HF versus healthy controls.^{4–11} Only few of these studies applied whole-brain analyses,^{4,5,7,10} while the others focused either on specific regions of interest, that is, hippocampus¹¹ and mammillary bodies,⁶ or were based on visual magnetic resonance imaging (MRI) assessment of brain alterations.^{8,9}

A consistent pattern of brain structural abnormalities emerges from previous investigations as recently summarized by Alosco and Hayes,¹² involving mainly the hippocampus and the surrounding medial temporal lobes, the thalamus, the middle and posterior cingulate cortex, the precuneus and widespread regions in the frontal, temporal and parietal lobes. Similar GM alterations have also been described as a consequence of HF in pediatric patients.¹³ Notably, this

pattern of brain changes closely resembles the one associated with Alzheimer disease,^{12,14,15} thus strengthening the notion that the association between HF and later Alzheimer disease might be mediated, at least in part, by region-specific structural brain changes. However, the underlying mechanisms leading to the observed brain changes remain unclear. Recent work focused on both brain structure and function and showed that HF was associated with both hippocampal GM loss¹⁶ and blood flow abnormality,¹⁷ suggesting a link between brain structural damage and decreased blood flow due to a decreased heart pumping efficiency.

Most of the up-to-date studies investigated how impairment of heart function and its consequences on blood circulation have an impact on brain structure by means of group comparisons between patients and controls. In our work, we aimed to provide a deeper insight into this topic, additionally focusing on the association between biomarkers for HF and brain GM changes in this case-control study. Namely, we studied ejection fraction (EF) and blood NT-proBNP (N-terminal prohormone of brain natriuretic peptide). The former, EF, is a well-established indicator of cardiac performance as it measures the proportion of diastolic volume ejected during ventricular contraction. Therefore, lower EF indicates poorer heart efficiency. The latter, NT-proBNP, is the inactive N-terminal fragment resulting from the cleavage of pro-BNP, a peptide released by myocardial cells in response to volume and pressure increases. Consequently, HF is associated with increased levels of NT-proBNP. Here, we measured HF biomarkers in patients with coronary artery disease (CAD) both at the time of patient hospitalization and after few years of follow-up to give an account of heart disease progression and long-term brain structural reorganization. We think that investigating correlations between these biomarkers and GM changes—using voxel-based morphometry (VBM)—would provide more sensitive results as compared with group comparisons and could help in further clarifying the relationship between HF and long-term GM structural alterations. Specifically, we hypothesized that EF is positively and NT-proBNP is negatively correlated with regional GM in the brain.

METHODS

Data Availability

Datasets analyzed during the current study are available on reasonable request. All data will be anonymized. MRI data will be available as gray matter density (GMD) images in the Neuroimaging Informatics Technology Initiative (NIfTI) format without any personal meta-data. All data will be shared in agreement with the European General Data Protection Regulation (GDPR).

Participants

A cohort of 80 patients (22 females; age, 54.9±5.3 years; mean±SD) participated in the study. The process of the

patients' recruitment and selection is shown in the supplement (Online Figure I). The initial visit of the total Leipzig heart study cohort (n=2884 patients with suspected CAD) was within a time period of 5.5 years (between December 2006 and July 2012).¹⁸ Patients were recruited to participate in this study within 1 year at the time of a follow-up measurement (between September 2012 and September 2013). In step 1, we identified 50 patients with CAD (here abbreviated as CAD+) combined with the highest NT-proBNP levels at the initial visit and suitability (in particular for MRI)/willingness to participate in an experimental session including magnetic resonance (MR) brain imaging and cognitive tests. In step 2, we matched 25 patients with CAD (here abbreviated as CAD−) and 25 patients without CAD (no abnormality detected [NAD]), both with normal NT-proBNP, respectively. Matching criteria included age, sex, diabetes mellitus, smoking status, carotid intima media thickness and carotid plaque presence. Finally, 80 patients (35 CAD+, 23 CAD−, and 22 NAD) were included in the MRI study. We excluded 20 cases, who missed the date of examination or whose examination resulted in data with insufficient quality. Note that all CAD+ patients showed NT-proBNP values above the confirmatory cut-point of 900 pg/mL to detect heart failure according to the guidelines of the European Society of Cardiology.¹⁹ However, in the CAD− group, 3 patients showed NT-proBNP values above the exclusionary cut-point of 300 pg/mL according to the European Society of Cardiology guidelines. Therefore, we excluded these 3 patients from all group analyses but included them when performing correlation analyses across all patients.

In all patients, investigations included several blood parameters, echocardiography, cardiac catheterization, thoroughly clinical and neuropsychological examination and MRI. The demographic, clinical, and neuropsychological data of the participants are listed in Tables 1 and 2. All patients were carefully checked for history of neurological or psychiatric diseases and screened for brain abnormalities. The majority of patients showed age-related changes in brain structure such as white matter lesions (see Fazekas score in Table 2). Three subjects presented lacunar or ischemic lesions with a maximum size of 2 cm. Note that lesions did not overlap regionally in different patients making a bias on our imaging study unlikely. Patients reporting potentially relevant diseases in their history did not show any brain changes after careful inspection of brain images. All other patients did not report any neurological or psychiatric diseases, and no brain lesions were detected in thorough inspection. All participants were carefully informed about the study and signed a written informed consent. The study was carried out in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the University of Leipzig.

In addition to the patients described above, a control cohort of 60 sex- and age-matched healthy participants (17 females; age, 52.2±6.3 years) was chosen from the population-based study of the Leipzig Research Centre for Civilization Diseases (LIFE).²⁰ These volunteers were scanned between January 2012 and October 2012 under identical conditions compared with the patients cohort (using exactly the same MR scanner and the same MR imaging parameters, see section below). In addition to brain imaging, EF and NT-proBNP values were also obtained for each control volunteer to exclude HF.

Table 1. Demographic Data of the Studied Subgroups

	Subgroups				Statistical Comparison (P)			
	LIFE	NAD	CAD–	CAD+	CAD+ vs CAD–	CAD+ vs NAD	CAD+ vs LIFE	ALL
Group size	60	22	20	35				
Females/males*	17/43	8/14	4/16	10/25	1.000	1.000	1.000	0.730
Age, y†	52.2±6.3	55.7±5.0	56.1±5.0	53.7±5.7	1.000	0.854	1.000	0.020‡

CAD indicates coronary artery disease; CAD+/CAD– group of CAD patients with/without heart failure; LIFE, group of healthy elderly participants of the Leipzig Research Centre for Civilization Diseases; and NAD, group of participants with nondetectable abnormality.

*Fisher exact test.

†ANOVA, post hoc analysis for pairwise group differences was generally controlled using Bonferroni correction (P values adjusted accordingly).

‡No significant result was obtained in the post hoc analysis for all possible group comparisons.

Clinical and Neuropsychological Examination

For all 80 patients, initial clinical examinations and blood serum markers were investigated right after hospitalization. Here, the standard examination procedure was performed including transthoracic echocardiography and blood sample investigation with the following markers: high sensitive troponin T, creatine kinase (CK), and isoenzyme muscle brain of creatine kinase (CK-MB), and NT-proBNP. After 3.5±1.3 years, EF and NT-proBNP were determined again with a follow-up measurement including an MRI session to obtain structural brain images (see Table 1 for the initial and the follow-up measurements of EF and NT-proBNP).

Cardiac function at baseline and follow-up was measured by standardized transthoracic echocardiography (Vivid q, GE Healthcare).¹⁸ Simpson's method was used to quantify left ventricular EF according to the European Society of

Cardiology-Recommendation for cardiac chamber quantification.²¹ In brief, EF was computed by biplane 2-dimensional measurements for end-diastolic (EDV) and end-systolic (ESV) left ventricular volumes as follows: $EF = (EDV - ESV) / EDV$. Healthy individuals typically show an ejection fraction ≥55%. NT-proBNP levels in the serum were measured using a Roche Modular analyzer (Roche Diagnostics, Germany). As aforementioned, individual levels of NT-proBNP were used to stratify the CAD patients into 2 groups of CAD+ and CAD– patients showing NT-proBNP values above 900 pg/mL and below 300 pg/mL, respectively.²² Vascular state of the carotid arteries was investigated with high-resolution ultrasound (Vivid q with a 12.0-MHz linear-array transducer, GE Healthcare). Carotid intima media thickness was measured with a semiautomated border detection program (GE Healthcare) and a simple carotid plaque score was performed as described before²³ by counting

Table 2. Cardiovascular Risk Factors and Clinical Data

	Subgroups			Statistical Comparison (P)		
	NAD	CAD–	CAD+	CAD+ vs CAD–	CAD+ vs NAD	ALL
Troponin T, pg/mL*	4.2±1.9	9.2±8.1	2388.2±1978.5	5.1·10 ⁻⁸	2.1·10 ⁻⁸	2.7·10 ⁻¹⁰
CK, µkat/L*	2.07±1.44	2.11±1.18	30.58±25.33	3.0·10 ⁻⁷	1.4·10 ⁻⁷	2.5·10 ⁻⁹
CK-MB, µkat/L*	0.26±0.06	0.25±0.05	3.70±2.74	1.5·10 ⁻⁸	6.7·10 ⁻⁹	6.4·10 ⁻¹¹
Gensini score*		21.3±14.3	48.6±27.9	1.6·10 ⁻⁴		
EF1*	62.5±5.4	63.7±5.4	47.2±11.7	1.4·10 ⁻⁸	4.9·10 ⁻⁸	2.0·10 ⁻¹⁰
EF2*	64.5±6.2	63.8±8.2	51.2±11.8	3.6·10 ⁻⁵	7.0·10 ⁻⁶	5.6·10 ⁻⁷
NT-proBNP1, pg/mL*	68.8±42.5	66.7±52.5	2758.8±1572.8	4.9·10 ⁻¹³	1.5·10 ⁻¹³	2.4·10 ⁻¹⁶
NT-proBNP2, pg/mL*	64.4±52.6	90.8±77.7	307.8±352.0	0.006	0.001	4.2·10 ⁻⁴
Arterial hypertension, yes/not	13/9	18/2	19/16	0.024	1.000	0.015
Diabetes mellitus, yes/not	5/17	4/16	9/26	1.000	1.000	0.941
Smoking, never/former/present†	8/7/7	5/10/5	7/20/8	0.870	0.516	0.449
Body mass index, kg/m ² *	27.9±4.0	28.4±4.2	28.7±4.1	1.000	1.000	0.767
Fazekas score, grade 0/1/2/3†	7/13/2/0	9/7/3/1	12/20/3/0	0.720	1.000	0.510
CIMT, mm*	0.77±0.18	0.72±0.10	0.69±0.15	1.000	0.130	0.126
Carotid plaque score, grade 0/1/2/3/4†	11/5/5/1/0	5/7/5/1/2	12/12/10/1/0	1.000	1.000	0.490
Attention, grade –2/–1/1†	0/11/11	0/11/9	1/19/15	1.000	1.000	0.962
Executive function, grade –2/–1/1†	2/12/7	0/9/11	2/17/16	1.000	1.000	0.556
Memory, grade –2/–1/1/2†	0/16/6/0	3/10/7/0	3/19/10/3	1.000	0.858	0.310

CAD indicates coronary artery disease; CAD+/CAD–, group of CAD patients with/without heart failure; CIMT, carotid intima media thickness; CK, creatine kinase; CK-MB, CK isoenzyme muscle brain; EF, ejection fraction (EF1 initial measurement, EF2 follow-up measurement); NAD, group of participants with nondetectable abnormality; NT-proBNP, N-terminal prohormone of brain natriuretic peptide (NT-proBNP1 initial measurement; NT-proBNP2 follow-up measurement); and Troponin T, high-sensitive troponin T.

*ANOVA, Post hoc analysis for pairwise group differences was generally controlled using a Bonferroni correction (P values adjusted accordingly)

†Fisher exact test.

segmental plaque presence of the common carotid artery and bulb resulting in values of 0 to 4.

Cognitive performance was assessed with a comprehensive test battery yielding for each of the patients' information for the cognitive domains attention, executive function, and memory at the follow-up measurement, that is, at the time of the MRI acquisition. Domains included the following neuropsychological tests: Attention: trail making test A, test battery of attentional processes (alertness, divided attention); executive function: trail making test B, hamasch 5-point test revised, Regensburg word fluency test, standardized Link's probe; memory: California verbal learning test, Rey-Osterrieth complex figure test. Individual raw values were transformed into age- and, if applicable, sex-matched normative values and categorized in comparison to normative controls in the following: -3 for far below average (<-2 SD), -2 for below average (≥-2 SD and <-1 SD), -1 for lower average (≥-1 SD and $<$ mean), 1 for upper average ($>$ mean and ≤ 1 SD), 2 for above average (>1 SD and ≤ 2 SD), and 3 for far above average (>2 SD).^{24,25} Mean averages were calculated for the 3 cognitive domains.

Statistical Analysis of Demographic and Clinical Data

To investigate potential differences between demographic and clinical parameters between the several subgroups, statistical analyses were performed using IBM SPSS Statistics Version 24. For all categorized demographic and clinical variables as sex, arterial hypertension, diabetes mellitus, smoking, carotid plaque score, white matter lesion score, and all cognitive parameters including attention, executive function, and memory, we looked at group differences with Fisher exact test to consider small sample sizes of the different subgroups. For all other continuous variables, group mean differences were investigated using an ANOVA. Post hoc analysis was performed looking at all pairwise group comparisons including Bonferroni correction for multiple comparisons using a significance level of $P<0.05$.

MRI Data Acquisition

Structural brain images were obtained using MRI with a 3 Tesla VERIO Scanner (Siemens Healthcare, Erlangen, Germany) and a 32-channel head array coil. Image acquisition was performed using a 3-dimensional magnetization-prepared rapid gradient-echo sequence with the syngo MR B17 software. Acquisition parameters were chosen using a flip angle of 9° , an echo time of 2.98 ms, an inversion time of 900 ms, a repetition time of 2300 ms, and a bandwidth of 238 Hz/Px. A sagittal slice orientation was chosen with 176 slices and an in-plane field-of-view with 240×256 mm². The nominal image resolution was set to $1 \times 1 \times 1$ mm³ with a final image matrix of $240 \times 256 \times 176$.

MRI Data Analysis

Structural brain images were processed using VBM.²⁶ GMD images²⁷ were computed using the computational anatomy toolbox (CAT 12) rev. 1184 (Structural Brain Mapping Group, University of Jena, Department of Psychiatry, Germany) with SPM 12 (The Wellcome Trust Centre for Neuroimaging, UCL, London, United Kingdom), and MATLAB (MathWorks, Inc, Natick, MA). GMD images were generated using the unified segmentation approach that presents a probabilistic framework

combining image registration, tissue classification, and bias correction.²⁷ Each voxel within the GMD images contains a measure of gray matter probability obtained by the unified segmentation approach. To account for volume changes during normalization, GMD was scaled by the amount of deformation that is also called modulation. To meet the assumptions of random field theory and to further account for the inter-subject variability, GMD images were finally smoothed with a gaussian kernel of 8 mm full-width at half-maximum.

Voxel-wise statistical analysis was performed with SPM 12 using the general linear model including age and total intracranial volume as covariates in the design matrix. Two-sample *t*-tests were implemented using the general linear model to do comparisons between all 3 subgroups of CAD+, CAD-, and NAD subjects. Note that these group comparisons did not include the 3 patients that were not classified according to the European Society of Cardiology guidelines. In addition to investigate group differences, correlation analyses were performed to test for a potential relationship between GMD and HF biomarkers using both the initial and the follow-up measurements of EF and NT-proBNP. Here, we looked for positive and negative correlations across the whole group of 80 participants. In all statistical analyses, clusters were detected using a voxel-threshold of $P<0.005$. To correct for multiple comparisons with multiple testing across all voxels of the GMD maps, a minimum cluster size was chosen to detect significant clusters with $P<0.05$, family-wise error corrected threshold on the cluster level.²⁸ This family-wise error correction was performed at whole-brain level, that is, for all multiple statistical tests of the same type within the image space. To visualize the correlation between brain structure and cardiac markers EF and NT-proBNP, respectively, we used GMD values for specific significant regions. Using the SPM software, we extracted both the uncorrected GMD values as well as the fitted GMD from the statistical model. Thereafter, we visualized the correlation between GMD and both parameters EF and NT-proBNP showing *r* and *P* values.

In addition to the parametric analysis, all statistical tests were repeated with state-of-the-art permutation tests using the threshold-free cluster enhancement (TFCE) technique²⁹ using the TFCE toolbox (Structural Brain Mapping Group, University of Jena, Department of Psychiatry, Germany) for SPM. This approach does not need an initial threshold to form clusters. Thus, in contrast to a 2-threshold approach, TFCE is sensitive for both focal and peripheral effects. Further, as the TFCE approach does not rely on the gaussian random field theory, it can handle images with varying local smoothness that is also called nonstationarity that makes TFCE the method of choice in VBM. We used the TFCE technique with 10 000 permutations and a significance level of $P<0.05$ (family-wise error-corrected).

RESULTS

Clinical Assessment

Demographic data are illustrated in Table 1. Statistical analysis did not reveal differences for sex and age between subgroups. Clinical values and cognitive parameters are shown in Table 2. In accordance with the definition of the subgroups, we found a significantly lower EF in the CAD+ group compared with the CAD- or

NAD groups, for both the initial and the follow-up measurement. However, we did not find any EF difference between the NAD and the CAD− patients for both the initial and the follow-up measurement. As defined, NT-proBNP levels were higher in the CAD+ group compared with either CAD− patients, or NAD subjects for the initial measurement. Interestingly, the NT-proBNP concentration was still increased with the follow-up measurement after 3.5 ± 1.3 years. Note that we did not find a significant difference in NT-proBNP between the NAD and the CAD− patients regarding both the initial and the follow-up value of NT-proBNP.

Beside EF and NT-proBNP, we also found increased levels of high sensitive troponin T, CK, and CK-MB when comparing CAD+ and CAD− patients, and when comparing CAD+ and NAD subjects. Between CAD− and NAD subjects, we found slightly increased troponin T values; however, we did not observe a significant difference when comparing CK and CK-MB between CAD− and NAD groups. We also assessed the intensity of CAD for both groups of CAD+ and CAD− patients using the Gensini score. Here, we found a significant difference between both groups as expected (Table 2).

We also analyzed the relationship between EF and NT-proBNP and found a significant negative correlation across the whole group of 80 subjects for both, the initial screening ($r = -0.59$; $P = 1.1 \cdot 10^{-8}$) and the follow-up measurement ($r = -0.45$; $P = 2.8 \cdot 10^{-5}$). Note that this correlation was significant only if all groups were included. We obtained $P > 0.01$ for all correlations between EF and NT-proBNP if analyzed separately in all 3 groups, that is, CAD+, CAD−, and NAD, for both the initial and the follow-up measurement—presumably due to low within-group variability.

We also looked at vascular risk factors, that is, the frequency of arterial hypertension, diabetes mellitus, and smoking as well as body mass index. Beside a difference in hypertension between the CAD− and the CAD+ group (that was probably induced by the fact that 20 out of 100 participants either missed the date of examination or showed insufficient data quality), we did not find any further significant group differences (see Table 2). Of note, the amount of white matter lesions as assessed with the Fazekas score and indicating small vessel disease did not significantly differ between all 3 groups. Carotid intima media thickness and the carotid plaque score did not show any significant differences between groups. Finally, neuropsychological performance as investigated in the cognitive domains attention, executive function and memory did not differ between groups (see Table 2).

Group Comparisons

Using the VBM technique with the magnetization-prepared rapid gradient-echo images, we looked at structural differences between all subgroups of participants,

namely between CAD+, CAD−, and NAD groups. Here, we found a significant difference of GMD between the CAD+ patients and the NAD subjects in wide regions of the cortex. In particular, we found a significant GMD decrease in the CAD+ patients across the whole brain including wide regions in the frontomedian cortex, in the parietal cortex, in the posterior cingulate cortex, and in the precuneus (Figure 1A). Note, that we also found a significant GMD decrease when comparing the CAD+ with the CAD− patients in the posterior cingulate cortex and in the precuneus (Figure 1B) in the same regions as found in the comparison between the CAD+ and the NAD subjects. However, the GMD differences between the CAD+ and the CAD− patients were much less widespread compared with the GMD differences between the CAD+ and the NAD subjects.

In addition to the comparisons between the CAD+ patients and the other 2 groups of CAD− and NAD subjects, we also investigated GMD differences between the CAD− and the NAD group. This comparison revealed a diminished GMD in CAD− patients in the left parietal cortex when using the parametric analysis. Although this finding might be interesting (as we also found a diminished GMD in the parietal cortex when comparing the CAD+ with the NAD group), we were not able to show this GMD difference using the nonparametric approach (therefore not shown). We also analyzed the inverse contrast of a possible GMD increase with HF within all group comparisons, that is, for the comparison between CAD+ and NAD, between CAD+ and CAD−, and between CAD− and the NAD. However, we did not find any significant GMD increase, neither with the parametric nor with the nonparametric approach.

We also performed group comparisons between the GMD images of the LIFE cohort consisting of healthy subjects and all 3 subcohorts of patients (CAD+, CAD−, and NAD). The comparison between healthy LIFE volunteers and CAD+ patients revealed major GMD differences in wide cortical and subcortical regions. Here, CAD+ patients showed decreased GMD across the whole brain including regions within the posterior and middle cingulate cortex (Figure 2A). These patients showed also significant GMD decrease in thalamus and hippocampus. Interestingly, the comparison between the LIFE participants and the other 2 subgroups of patients, namely, CAD− and NAD, did not reveal major GMD differences as shown in Figure 2B and 2C, respectively. Note that we also performed all tests with the opposite contrast, that is, searching for a GMD increase in the 3 subgroups of patients compared with the LIFE cohort. However, we did not find a GMD increase in any of the 3 subcohorts, neither with the parametric nor with the nonparametric approach.

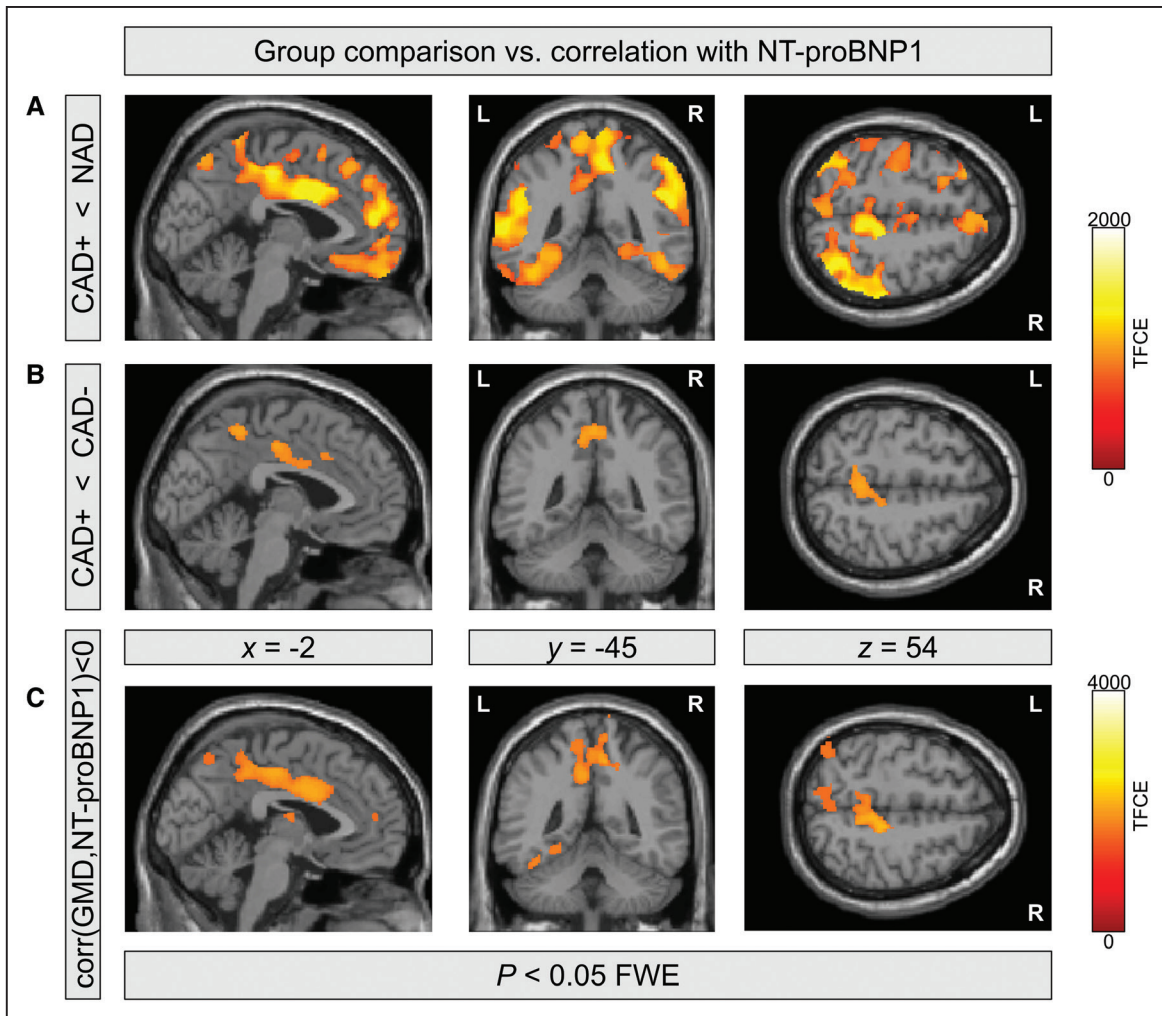


Figure 1. Orthogonal brain sections showing significant differences in gray matter density (GMD) with heart failure.

A, Comparing coronary artery disease (CAD) patients with heart failure (CAD+, $N=35$) and participants with no detectable abnormality (NAD, $N=22$) reduced GMD values were found across the whole brain including a region within the posterior and middle cingulate cortex (respectively, PCC and MCC). **B**, The comparison between CAD+ patients and CAD patients with sufficient heart function (CAD-, $N=20$) showed reduced GMD in the same regions, namely the PCC and MCC. **C**, A negative correlation between GMD and the serum NT-proBNP (N-terminal prohormone of brain natriuretic peptide) concentration (initial measurement, NT-proBNP1) was found across the whole group of participants ($N=80$). Reduced GMD was related to higher NT-proBNP concentrations in the PCC and MCC up to regions within the precuneus. Results were obtained with threshold-free cluster enhancement (TFCE) with $P < 0.05$ using family-wise error (FWE) correction for multiple comparisons.

Correlation Analysis With HF Biomarkers

In line with our findings about structural differences between all groups (Figure 1A and 1B), we also found a significant negative correlation between GMD and the initial measurement of NT-proBNP across all 80 participants. This negative correlation was found in the same regions as obtained with both group analyses comparing CAD+ with NAD subjects, and comparing CAD+ with CAD- patients, namely in the posterior cingulate cortex and in the precuneus (Figure 1C). Higher levels of NT-proBNP were associated with a significant decline of GMD in these brain regions. Interestingly, this result was not obtained when using the follow-up measurement of NT-proBNP instead of the initial measurement. Using the follow-up

measurement, we obtained a significant negative correlation between NT-proBNP and GMD only in the vicinity of the left hippocampus (Figure 3B and 3C). The same region was also found when looking for GMD differences between the CAD+ and the NAD groups (Figure 3A). Figure 3B and 3C shows this negative correlation between GMD and the follow-up measurement of NT-proBNP with both the nonparametric and the parametric approach, respectively. The dot-plot of Figure 3D shows the negative correlation between GMD and the follow-up measurement of NT-proBNP for the left hippocampus. Here, the red points show the fitted GMD within the statistical model while the black dots show the uncorrected GMD values.

Note that we did not find any significant positive correlation between GMD and NT-proBNP across the

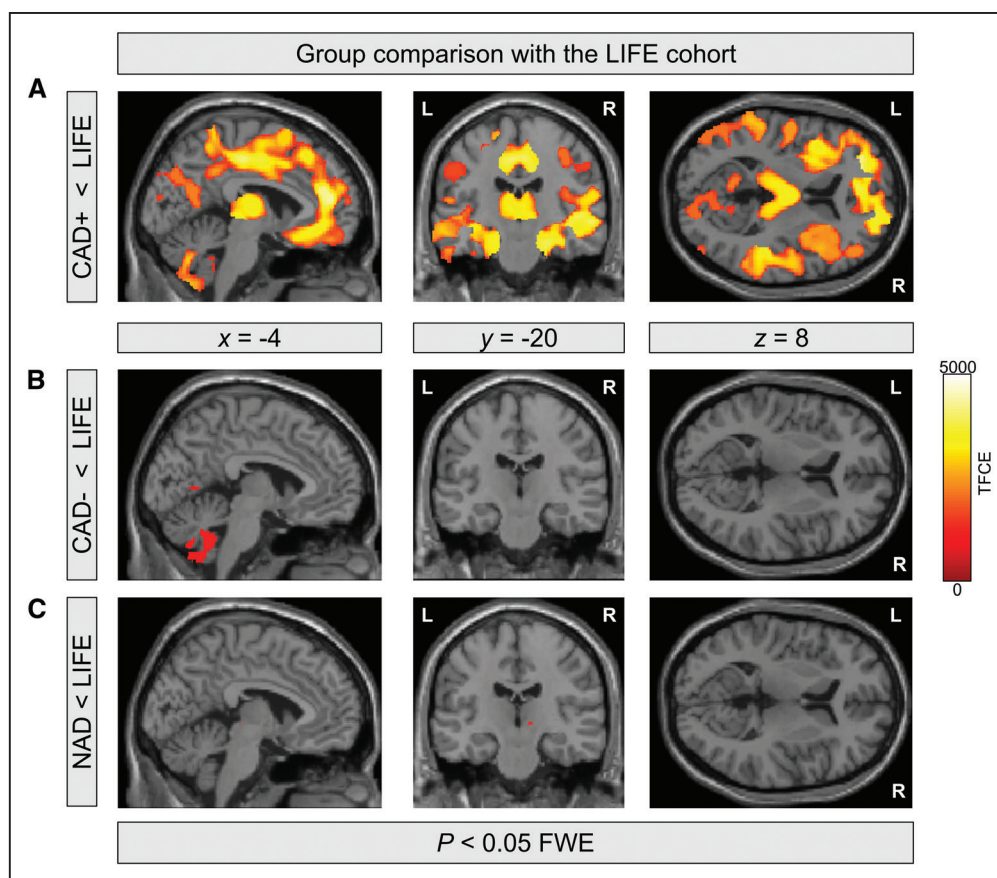


Figure 2. Orthogonal brain sections showing significant differences in gray matter density (GMD) between heart failure patients and healthy controls from the Leipzig Research Centre for Civilization Diseases (LIFE) cohort.

A, Comparing coronary artery disease (CAD) patients with heart failure (CAD+, $N=35$) and healthy volunteers (LIFE, $N=60$) reduced GMD values were found across the whole brain including a region within the posterior and middle cingulate cortex (respectively, PCC and MCC). In addition, we also obtained reduced GMD values in subcortical brain regions as thalamus and hippocampus. The comparison between the healthy LIFE volunteers and the other 2 patients subcohorts (**B**, LIFE volunteers vs CAD patients with sufficient heart function, CAD-, $N=20$; and **C**, LIFE volunteers vs patients with no detectable abnormality, no abnormality detected [NAD], $N=22$) did not reveal major GMD differences. Results were obtained with threshold-free cluster enhancement (TFCE) with $P < 0.05$ using family-wise error (FWE) correction for multiple comparisons.

whole brain, neither with the initial nor with the follow-up measurement of NT-proBNP. We used both the parametric and the nonparametric approach to detect such a positive relationship. However, we did not obtain any significant result.

Beside the marker NT-proBNP for the assessment of HF, we also performed correlation analyses between EF and GMD to investigate a potential relationship between a reduced pumping efficiency with HF and a GMD decline. We found a significant positive correlation between GMD and the initial EF measurement in the entire frontomedian cortex (including regions of the orbitofrontal cortex) extending to the posterior cingulate cortex and precuneus (Figure 4B; Figure 5A and 5C). This positive correlation showed the same pattern like the GMD decline in the CAD+ group compared with the NAD one (Figure 4A). Interestingly, when using the follow-up measurement instead of the initial value of EF, there was no significant correlation present anymore except in the left and right orbitofrontal cortex

(Figure 5B) and in the precuneus (Figure 5D). Thus, the follow-up EF measurement turned out to be less sensitive for detecting GMD changes associated with HF. Nevertheless, both the initial and the follow-up EF measurement showed a significant positive relationship with GMD in both the left and right orbitofrontal cortex. Figure 6 shows this positive GMD-EF correlation for the right orbitofrontal cortex using a parametric approach showing that a reduced EF is associated with a diminished GMD. Interestingly, this positive correlation (within the left and right orbitofrontal cortex) can be shown with both the initial and the follow-up EF measurement (Figure 6A and 6B, respectively). In the dot-plots, red points show the fitted GMD within the statistical model while the black dots show the uncorrected GMD values.

In addition to the detected positive relationship between EF and GMD, we also investigated a potential negative correlation. However, we did not find any significant negative EF-GMD correlation across the

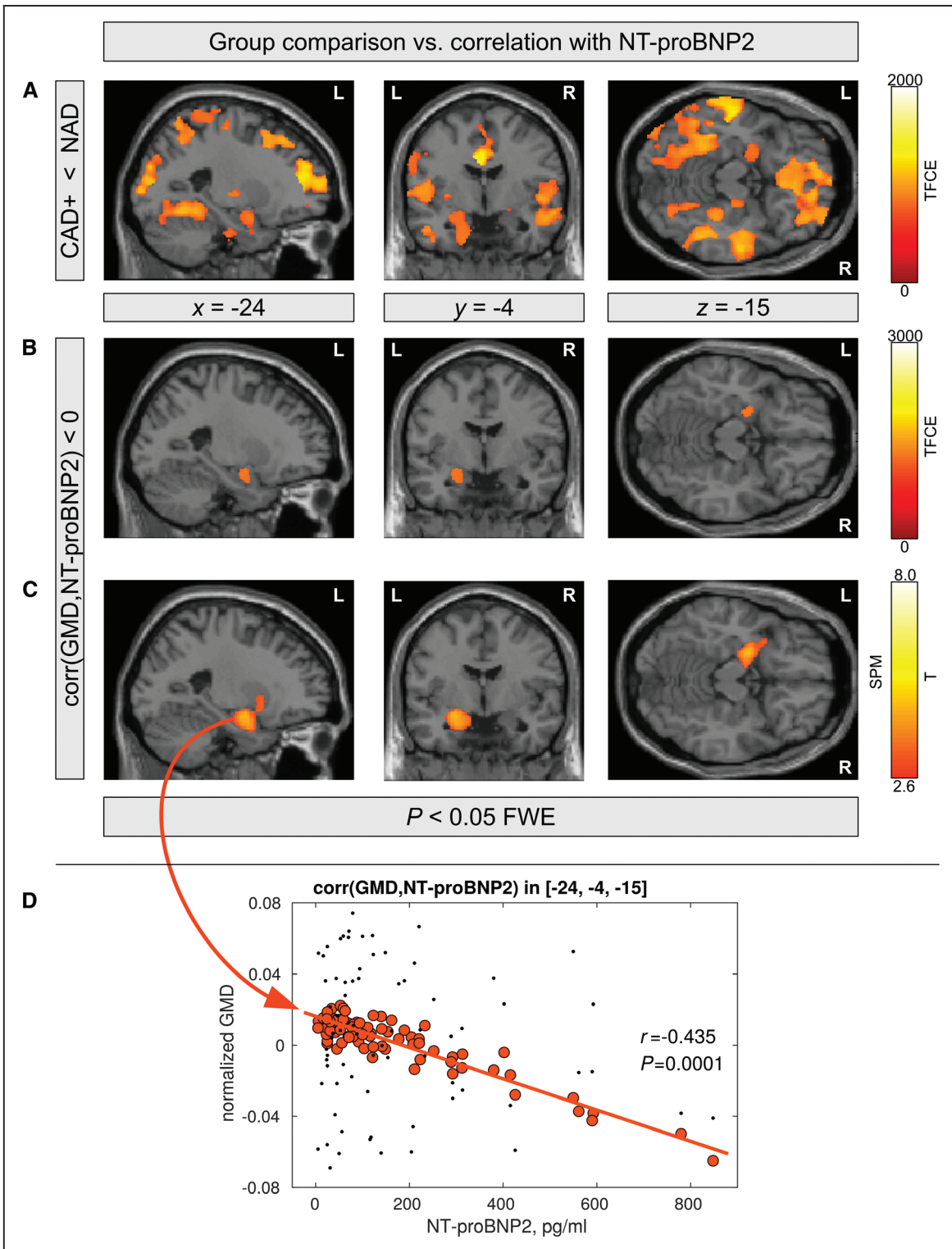


Figure 3. Orthogonal brain sections showing a comparison between gray matter density (GMD) group differences and correlations between GMD values and concentrations of serum NT-proBNP (N-terminal prohormone of brain natriuretic peptide). **A**, Reduced GMD was observed across the whole brain in patients with coronary artery disease (CAD) with heart failure (CAD+, N=35) compared with participants who showed no abnormality (no abnormality detected [NAD], N=22). **B**, A correlation analysis revealed a negative association between GMD and serum NT-proBNP concentrations (follow-up measurement, NT-proBNP2) across the whole group (N=80) in the left hippocampus. **C**, The parametric approach showed the same result as obtained with permutation tests as shown in (B). **D**, Dot-plot showing the negative correlation between GMD and serum NT-proBNP2 in the left hippocampus revealed with the parametric analysis. The red points show the fitted GMD within the statistical model while gray dots show the uncorrected GMD values. FWE indicates family-wise error.

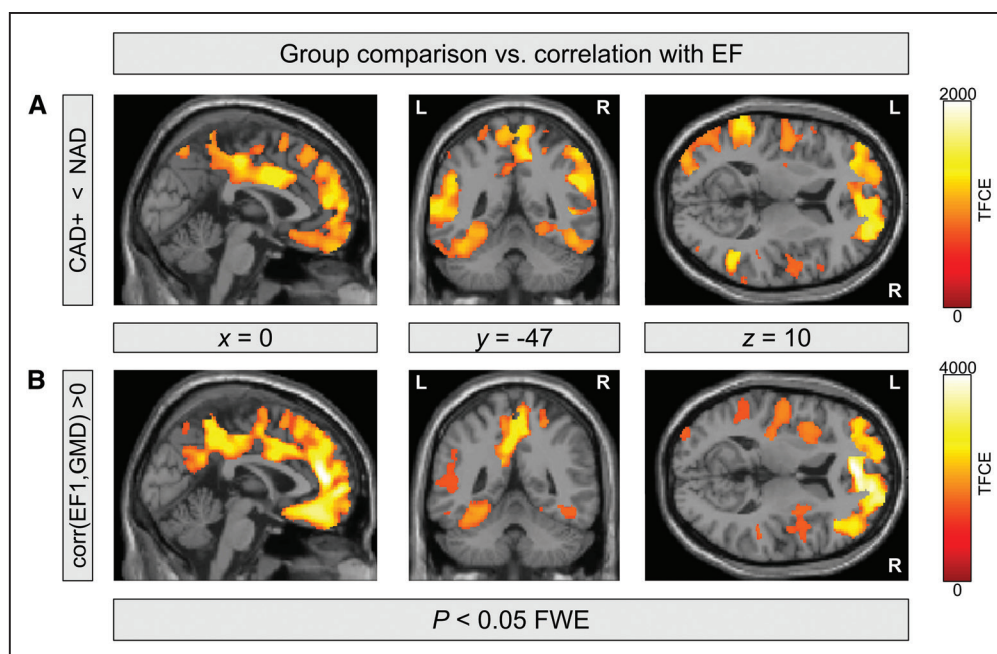


Figure 4. Orthogonal brain sections showing a comparison between gray matter density (GMD) group differences and correlations between GMD and ejection fraction (EF).

A, Reduced GMD values were observed across the whole brain in patients with coronary artery disease (CAD) with heart failure (CAD+, $N=35$) compared with participants who showed no abnormality (NAD, $N=22$). In particular, reduced GMD was found in major parts of the median cortex as well as in frontal and prefrontal brain regions. **B**, Positive correlation between GMD and EF was found across the whole group ($N=80$, bottom row) in similar brain regions obtained with the group comparison as shown in (**A**). Results were obtained with threshold-free cluster enhancement (TFCE) with $P < 0.05$ using family-wise error (FWE) correction for multiple comparisons.

whole brain, neither with the initial nor with the follow-up EF measurement. We used both the parametric and the nonparametric approach to detect such a negative correlation. However, we did not find any significant result.

DISCUSSION

Our study shows that patients suffering from HF present detrimental GMD decline in the brain years after the emergence of the condition. In brief, both the group comparisons and the correlation analyses with biomarkers for HF showed convergent results, revealing the most consistent GMD decline in the precuneus/cingulate cortex, in the hippocampus and in the orbitofrontal cortex. In the following, we discuss the results of the group comparison analysis, the correlations with biomarkers for HF, and their overlap.

Group Comparisons

We observed a significant pattern of GMD decline associated with HF predominantly in posterior and middle cingulate cortex and precuneus. This GMD reduction was obtained in both group comparisons, between CAD+ and NAD, and between CAD+ and CAD- patients. Interestingly, the observed GMD differences

were much more widespread in the CAD+ versus NAD comparison, including also regions in the whole medial cortex, encompassing the frontomedian cortex, the orbitofrontal cortex and the medial temporal lobes. In contrast, the CAD+ versus CAD- comparison only showed a more focal decline in the posterior and middle cingulate cortex and in the precuneus. Thus, the overlap of both group comparisons (namely the posterior and middle cingulate cortex and the precuneus) reflects the brain regions mostly affected as a consequence of HF. This finding is in line with previous research investigating the effect of HF onto brain structure. Indeed, several papers reported structural brain differences in the cingulate cortex when comparing patients with HF with healthy controls.^{4,5,10,30,31} Results were confirmed in a comparison to another independent healthy cohort from the LIFE study.

One could object that results of this comparison might just reflect stronger vascular impairment in the brain in the CAD+ compared with the CAD- group (and NAD group) rather than being a consequence of HF. Although this is a reasonable line of arguments, our results make this hypothesis unlikely. Comparing the 3 groups, we did not find any differences for small vessel disease as assessed with the Fazekas score and for the vascular state of the carotid arteries as investigated with carotid intima media thickness and carotid plaque score. Furthermore, we did not find consistent differences between

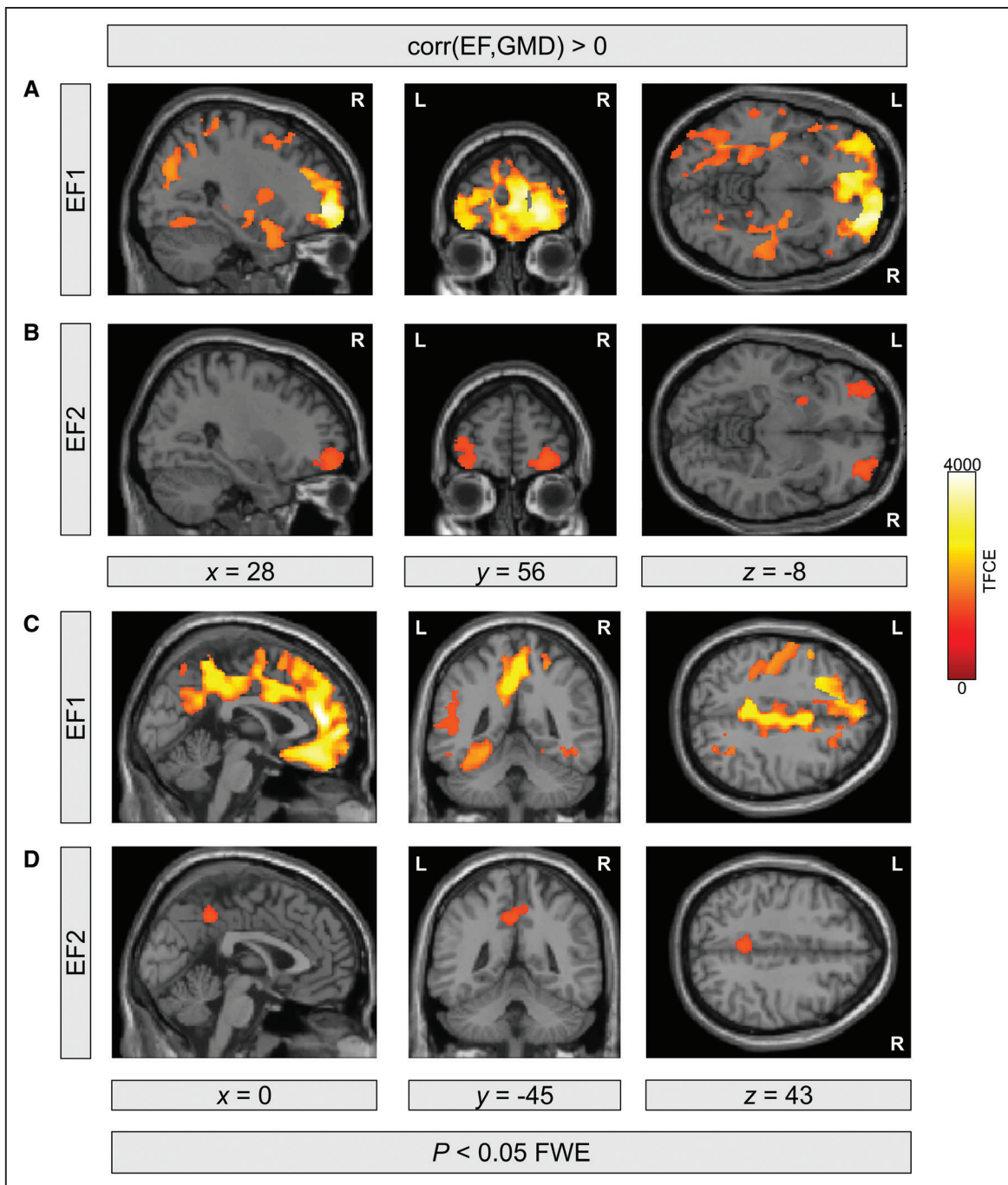


Figure 5. Orthogonal brain sections showing the correlation between brain's gray matter density (GMD) and the ejection fraction (EF) of the heart across the whole group of 80 participants.

A and **B**, Positive correlation was found in the left and right orbitofrontal cortex using both the initial (EF1, see **A**) and the follow-up EF measurements (EF2, see **B**). **C** and **D**, Positive correlation was also obtained in the whole frontal and parietal medial cortex when using the initial EF measurement (EF1, see **C**). Using the follow-up EF measurement (EF2), this correlation was only left in the precuneus (see **D**). Significant clusters were obtained using a nonparametric permutation approach using threshold-free cluster enhancement (TFCE) with a family-wise error (FWE) corrected $P < 0.05$.

groups for cardiovascular risk factors such as smoking, obesity, and diabetes mellitus after correction for multiple comparisons. The only difference we found was a higher number of patients with arterial hypertension in the CAD− group compared with the CAD+ group; however, this did not compromise our results if we expect

a higher degree of brain atrophy with hypertension.³² In fact, we found a diminished GMD in CAD+ patients compared with the CAD− group.

Note that a few patients in the CAD+ group showed lacunar/ischemic lesions as expected; however, they did not overlap regionally making a bias on our results

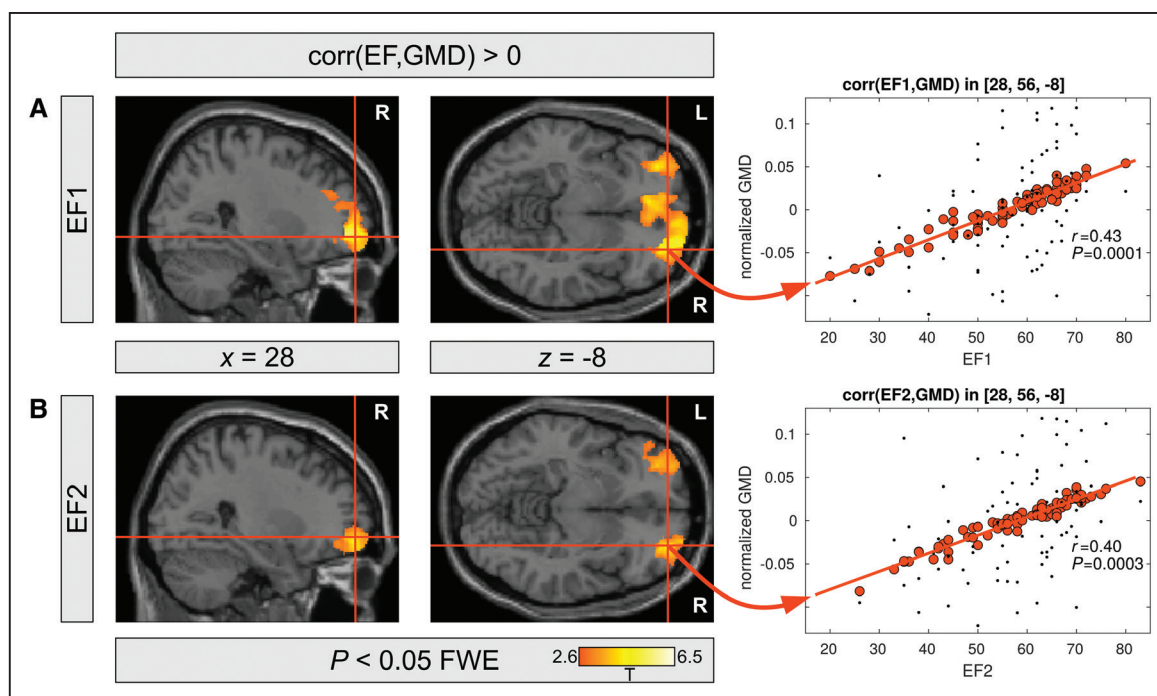


Figure 6. Orthogonal brain sections showing a positive correlation between the heart ejection fraction (EF) and the brain's gray matter density (GMD) across the whole group of 80 participants using a parametric approach with the general linear model (GLM).

Significant clusters were obtained in same regions as revealed with nonparametric permutation tests (see Figure 5). The dot-plots show the correlation between EF and GMD in the right orbitofrontal cortex using both the initial (ejection fraction, initial measurement [EF1], see [A]) and the follow-up EF measurements (ejection fraction, initial measurement [EF2], see [B]). The red points show the fitted GMD within the statistical model while gray dots show the uncorrected GMD values.

unlikely. In conclusion, brain atrophy in patients with coronary disease and HF is mainly related to HF and not vascular brain disease. Another option to solve this possible interaction between HF and coronary disease would have been including a patient cohort with HF but without coronary disease. However, this strategy might add other biases related to different etiological mechanisms. One might further criticize that our results are based on a cross-sectional approach without having baseline MRI measurements, that is, before the beginning of CAD and/or HF, available. Although a limitation, we controlled for possible biases by excluding interactions with vascular risk factors and changes of brain vasculature, and by adding a comparison to a healthy independent cohort to underline the validity of our findings.

Remarkably, the precuneus and posterior cingulate cortex have been discussed to be involved in the most frequent neurodegenerative disease—Alzheimer disease—leading to a decline in memory function.^{33,34} This has been validated implementing meta-analytical approaches that have shown decreases of glucose metabolism and perfusion in these regions.¹⁵ Such brain alterations are evident not only in Alzheimer dementia, characterized by impairments in everyday life, but already in its prestage—mild cognitive impairment—where cognitive deficits are detectable in neuropsychological investigations without evident everyday life alterations. Beside these functional

changes, the same meta-analysis revealed regional atrophy in the hippocampus, entorhinal cortex and amygdala in Alzheimer dementia, and in the rectal gyrus in mild cognitive impairment, as well as hypometabolism and hypoperfusion in the angular and supramarginal gyrus. These brain regions are also impaired by HF, as evident from our group comparison between CAD+ and NAD subjects. The fact that CAD is common to both CAD+ and CAD− subjects could be considered as a confounding factor when comparing CAD+ and NAD because the CAD+ versus CAD− comparison revealed regionally more focused effects. However, according to our results, CAD without HF does not have an impact on brain structure, as evident from the comparison between the CAD− and NAD groups that revealed inconsistent results.

In line with these facts and as aforementioned in the introduction, Alosco and Hayes¹² discussed that the increased risk for Alzheimer disease in patients with HF might be mediated by specific structural brain alterations. The authors reviewed structural MRI studies in patients with HF and revealed neural atrophy and white matter alterations in the Papez circuit, that is, hippocampus, cingulate gyrus, thalamus, mammillary bodies, and fornix, and cortical and cerebellar regions that are also involved in Alzheimer disease. The authors discuss that reductions in cerebral blood flow due to HF might lead to structural brain changes. Indeed, patients with HF show reduced

cerebral blood flow in regions involved in Alzheimer disease, such as hippocampus, parahippocampal gyrus, and posterior cingulate cortex.¹² For example, Alves and colleagues reported significant cerebral blood flow reduction in patients with HF compared with controls in posterior brain regions, encompassing the cuneus, precuneus, posterior cingulate cortex, and right temporo-parietal associative areas.³⁵ Similar findings strengthen the hypothesis that the link between HF, brain structural changes and increased risk for Alzheimer disease might be mediated by altered brain perfusion. Indeed, brain hemodynamic abnormalities could lead to a shortage of glucose and oxygen to the brain that would in turn trigger a cascade of adverse biochemical events eventually leading to metabolic and tissue damages.^{1,36,37} However, other mediators of the association between HF and GM injury have been proposed, including pathological changes in the neuro-hormonal axis, increased inflammation, and nutritional (thiamine) deficiency.³⁸ Of note, vascular dysfunction is considered as an important early event in Alzheimer disease now, at least partly mediated by vascular risk factors such as arterial hypertension.^{32,39,40} Future studies shall disentangle the interplay between cardiovascular risk factors such as HF and development of Alzheimer disease by applying multimodal amyloid and MR imaging in longitudinal studies and considering also genetic risk factors such as apolipoprotein E status. As cognitive impairment was generally rather low in our cohort without significant group differences (Table 2), one might hypothesize that HF makes patients' brains more sensitive to alterations by Alzheimer disease and lead to relevant cognitive deficits at least in the long run; however, this hypothesis has to be proven by future longitudinal studies.

In addition to the described GM damages, previous studies also investigated the consequences of HF on white matter integrity using different MRI sequences. For example, brain changes were also found with detecting an increase in T2 relaxometry,³¹ a measure for brain tissue injury, in patients with HF compared with controls. Additionally, Kumar et al^{6,30} also described widespread white matter changes related to HF by means of diffusion tensor imaging MRI. These findings corroborate the view of HF as a deleterious circumstance for the entire brain structural organization.

Correlation Analysis With HF Biomarkers

We obtained significant correlations between brain structure and both the investigated HF biomarkers, EF, and NT-proBNP. As hypothesized, GMD was positively correlated with EF and negatively correlated with NT-proBNP. We identified only a previous study that investigated the relationship between HF biomarkers and brain structural changes.⁹ In particular, Vogels and colleagues reported a positive correlation between left ventricular EF and total white matter hyperintensities in the brain but no

correlation between NT-proBNP and brain structural alterations. However, it has to be noted that the definition of brain structural abnormalities was performed by visual assessment of individual MRI scans, while, in our study, we employed state-of-the-art MRI quantitative analysis. We found that a diminished GMD correlated with decreased EF at the baseline in several brain regions, ranging from frontomedian regions (including the orbitofrontal cortex) to the posterior cingulate cortex and precuneus. This pattern resembles very closely the one identified by the group comparison (CAD+ <NAD). Of note, the correlation between GMD and EF at follow-up was significant only in the orbitofrontal regions. This observation is in line with previous work showing a reduced cortical thickness in patients with HF in these cortical regions.⁷ We note that the orbitofrontal cortex plays a substantial role in blood pressure regulation,⁴¹ which might link reduced EF, potentially diminished blood flow, and structural brain changes.

Increased NT-proBNP at baseline correlated with diminished GMD in the posterior and middle cingulate cortex and precuneus, thus confirming once again the association between these brain regions and HF. The NT-proBNP follow-up values instead negatively correlated with GMD in the hippocampus in our patient cohort. Structural abnormalities in the hippocampus were previously shown in rats with HF using VBM and probabilistic maps of the Wistar rat brain.¹⁶ In line with these observations, histological analysis revealed a decreased neurogenesis together with an increased number of astrocytes in the ventral hippocampus of these HF rats compared with sham rats.¹⁶ Thus, the relationship between NT-proBNP concentrations and GMD might reflect brain injury due to changes in hippocampal blood flow in HF.¹⁷ As in the case of EF, the results of the correlation analyses were also identified when comparing CAD+ patients to NAD individuals. However, focusing on the biomarkers at different time points add a more fine-grained perspective to our results. In particular, the correlations with follow-up measures identify the brain regions that are more impaired in subjects with a poorer prognosis.

Notably, for both HF biomarkers, we observed reductions in the spatial extent of the correlation patterns between baseline and follow-up measures. The baseline measure reflects the acute state, characterized by higher score variability, while the follow-up captures the disease progression in the chronic state. We propose that baseline measures correlate well with brain GM changes at follow-up because HF-induced plastic changes in the brain are in this case slow. Moreover, the more focal correlations between GMD and HF measures at follow-up might indicate that the patients with persistent impairment in EF and NT-proBNP show more severe brain impairment in the long term. In other words, when EF and NT-proBNP persist in a worse state, the orbitofrontal cortex, the hippocampus, and the precuneus show more severe structural damage. Overall, our findings show that

the biomarkers for HF that are used to classify patients in the clinic also reflect specific brain structural changes.

Limitations of the Study

Finally, we want to discuss possible limitations of our study. In selecting patients from a large cohort with suspected CAD (see Methods section), our inclusion criteria might have led to a selection bias, because patients had to be suitable for MRI investigation excluding by definition for instance patients with pacemakers. Moreover, CAD is generally associated with vascular risk factors that might also alter brain function and lead to stronger impairment in the CAD+ group. We controlled for this possible bias by showing no substantial differences of vascular risk factors, vascular state of the carotid arteries and white matter lesions between the groups. Only arterial hypertension was observed more frequently in CAD− than CAD+, which was not relevant for our results due to the direction of that difference. Although a few patients in the CAD+ group showed lacunar/ischemic lesions as expected, they did not overlap regionally making a bias on our results unlikely. This possible bias was further controlled for by re-analyzing data after excluding relevant patients with ischemic lesions. This re-analysis also confirmed the stability of our findings. Although the number of patients involved in our study is reasonable, future studies shall prove our findings in different and larger cohorts. This point is particularly relevant to validate the assumed connection between heart failure, cerebral hypoperfusion, structural brain damage and cognition, which can only be done in longitudinal studies including further imaging methods that are sensitive to blood flow changes or amyloid deposition.

CONCLUSIONS

Our study confirms that patients who suffered from HF undergo detrimental brain structural changes. Moreover, we show the usefulness of including biomarkers for HF to further disentangle the brain regions that are more affected in the chronic state, that is, the precuneus, the left hippocampus, and the orbitofrontal cortex. Further research is needed to clarify the relationship between these brain structural changes and the emergence of diseases of late life, first and foremost cognitive deficits or dementia due to Alzheimer disease.

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Disclosures

None.

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