Cognitive and brain changes associated with ischaemic heart disease and heart failure

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Aims
It is unclear whether the cognitive dysfunction associated with heart failure (HF) is due to HF or comorbid conditions such as ischaemic heart disease (IHD). This study aimed to determine whether, compared with controls with and without IHD, adults with systolic HF show evidence of cognitive impairment and cerebral grey matter (GM) loss.

Methods and results
Cross-sectional study of 35 participants with HF, 56 with IHD, and 64 controls without either HF or IHD. Subjects were older than 45 years and free of overt cognitive impairment. We acquired magnetic resonance images and used SPM8 to determine regional differences in cerebral GM volume. Participants with HF had lower scores than controls without IHD, adults with systolic HF show evidence of cognitive impairment and cerebral grey matter (GM) loss.

Participants with HF had lower scores than controls without IHD on immediate memory, long delay recall and digit coding, whereas those with IHD had lower long delay recall scores than controls without IHD. Compared with controls without IHD, participants with HF showed evidence of GM loss in the left cingulate, the right inferior frontal gyrus, the left middle and superior frontal gyri, the right middle temporal lobe, the right and left anterior cingulate, the right middle frontal gyrus, the inferior and pre-central frontal gyri, the right caudate, and occipital-parietal regions involving the left precuneus. The loss of GM followed a similar, less extensive, pattern when we compared participants with HF and IHD.

Conclusion
Adults with HF have worse immediate and long-term memory and psychomotor speed than controls without IHD. Heart failure is associated with changes in brain regions that are important for demanding cognitive and emotional processing.

Keywords
Heart failure • Ischemic heart disease • Coronary disease • Memory • Cognition • Cognitive • Function • Magnetic resonance imaging • Brain

Introduction
Heart failure (HF) is a common consequence of most diseases of the heart, and nearly 9 in every 10 cases are associated with the presence of ischaemic heart disease (IHD) or hypertension.¹ Current estimates suggest that about 3% of adults have HF and its prevalence in the community is expected to rise as the population ages.² Heart failure is a leading cause of mortality worldwide,³ and survivors often experience declining physical and mental health.⁴ Depression and cognitive impairment are the most frequent mental health problems among people with HF.⁵,⁶

Systematic reviews of observational studies found that people with systolic HF perform less well than controls on measures of general mental ability, attention, and memory,⁷,⁸ although data on this topic remain sparse and deficits may be due to co-occurring conditions, such as IHD or cerebrovascular disease.⁶,⁹ Some investigators have suggested that cognitive deficits in HF are a consequence of reduced systolic output,¹⁰–¹² or, alternatively, that they reflect a generalized pattern of decline in functional capacity.¹³ Others proposed that these difficulties arise because of reduced cerebral perfusion or ischaemic damage to the brain.¹⁴,¹⁵
Woo et al. examined magnetic resonance images (MRI) of 9 people with HF and 27 controls. They found that participants with HF showed evidence of reduced cerebral grey matter (GM) volume in the insula, basal ganglia, cingulate gyrus, parahippocampal gyrus, dorsal midbrain, ventral and superior frontal cortex, and bilateral parietal and lateral parietal–occipital cortex, although interpretation of these results is hampered by the small sample size, non-availability of concurrent cognitive measures, and lack of a control group with cardiovascular disease but no HF. The latter would have allowed the investigators to clarify if the brain changes that they observed were specific to HF.

The question of whether HF is causally related to structural brain changes and cognitive decline is important because current approaches to the management of HF require the active participation of patients, who are expected to adhere to a complex treatment regime. The concern is that patients may have trouble complying with medical advice, which would lead to suboptimal management, more frequent health complications, and greater use of health services. Moreover, a better understanding of the association between HF and cognitive impairment may enhance our appreciation of the mechanisms that link cardiovascular diseases to cognitive decline in later life.

We designed the present study to determine whether adults with systolic HF show evidence of: (i) cognitive impairment compared with controls with and without established history of IHD, and (ii) cerebral GM loss compared with controls with and without established history of IHD. We hypothesised that participants with HF would attain lower scores than controls with and without IHD on tests of general intellectual function, memory, and psychomotor speed. We also expected participants with HF to show evidence of GM loss compared with controls with and without IHD, particularly in brain regions involved in the regulation of psychomotor speed, attention, and memory. Finally, we hypothesised that participants with IHD would show no evidence of cognitive impairment or GM loss compared with cardiomatically healthy controls.

**Methods**

**Study design**

We completed a cross-sectional study of adults with HF, IHD, and controls. We collected endpoints of interest between May 2006 and March 2009 in Perth, Western Australia.

**Participants**

Participants were community volunteers who responded to advertisements about the study in the local media, or were referred for assessment by their primary care physicians or hospital consultants. The Ethics Committees of the Royal Perth, Fremantle and Sir Charles Gairdner Hospitals approved the study protocol and participants offered written informed consent. The Declaration of Helsinki for Human Rights guided all activities of this study.

We excluded from participation people with past history of stroke or cardiac arrest, hearing or visual impairment, Mini-Mental State Examination (MMSE) score < 24, or who showed evidence of clinically significant depressive or anxiety symptoms [Hospital Anxiety and Depression Scale (HADS) sub-scores > 10]. We also excluded volunteers younger than 45 years of age, and those who were not fluent in written/spoken English, who reported recent myocardial infarction (≤30 days), who were unwilling/unable to undergo a MRI scan of the head, or who showed imaging evidence of brain tumours or cortical strokes.

Participants with established diagnosis of HF before enrolment into the study showed evidence of left ventricular dysfunction at the time of recruitment (ejection fraction—EF < 0.4) and clinical symptoms consistent with the diagnosis of HF for at least 6 months, such as exertion dyspnoea, orthopnoea, fatigue and weakness, dry cough, dizzy spells or palpitations, or physical signs of systemic oedema (CHF group). We excluded adults with New York Heart Association Functional Classification (NYHA) class IV because of marked disability and high short-term mortality. Hence, our HF participants had treated and stable illness.

Controls with IHD had documented clinical and biochemical evidence of past myocardial infarction (i.e. elevated CK, CKMB, troponin T, or troponin I), normal left ventricular function (EF > 0.6), and no clinical symptoms of HF. The procedures that we used to obtain these data have good sensitivity and specificity. Controls without overt IHD denied symptoms or history suggestive of angina, myocardial infarction, and HF, and had normal left ventricular function (EF > 0.6) (healthy controls).

The participants of this study did not overlap with those who took part in the pilot project that we have previously reported. The Cambridge Cognitive Examination of the Elderly Revised (CAMCOG) was the primary outcome measure of this study. The CAMCOG is a valid and reliable brief neuropsychological battery that assesses various aspects of cognitive functioning, including orientation, language, memory, attention and concentration, praxis, perception, calculation, and executive functions. The assessment produces a total summary score that can range from 0 to 105, with higher scores indicating better performance. Normative data show that the mean score for people of similar age and education is about 94 points with a standard deviation of 9. Other cognitive outcomes included immediate, and short- and long-delayed recall (memory) as measured by the California Verbal Learning Test (CVLT), and the Digit Copy and Coding subtests of the Wechsler Adult Intelligence Scale. The latter is a measure of psychomotor speed and attention. Normative data for the CVLT show that the expected standard deviation for immediate, short-, and long-delayed recall is about 11.5, 3.5, and 3.0 points, respectively.

**Outcome: cognitive function**

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**Outcome: cerebral grey matter volume**

We used a 1.5 Tesla Siemens Symphony MRI scanner [TR: 2830 ms, TE: 4.48, flip angle: 15, matrix size: 256 × 256 × 172, voxel size: (0.9 mm)³] to acquire DICOM data, which were converted to NIFTI file format using MRlcron (http://www.mricron.com). We used Statistical Parametric Mapping version 8 (SPM8, release 4010) to process the data on Matlab® 2010b (version 7.11.0.584) and Windows 7 64-bits. A detailed description of the methods used to analyse the images appears in the Supplemental Material.

**Other measures**

We measured symptoms of depression and anxiety with the HADS. Participants provided information about their age, gender, marital status, and schooling (highest degree achieved), as well as about their clinical history of hypertension, diabetes, and dyslipidaemia. We assessed pre-morbid intelligence quotient (IQ) with the Cambridge
Contextual Reading Test, and calculated the left ventricular EF based on the results of an echocardiogram (Perth Echo Services). Participants completed the 6 Min walk test.

We used standard commercial biochemical tests to measure serum B-type natriuretic peptide (BNP), tumour necrosis factor alpha (TNF-α), cortisol, interleukin-6 (IL-6), and total plasma homocysteine (tHcy). B-type natriuretic peptide concentrations \( \geq 100 \) pg/mL indicate the presence of myocardial dysfunction and HF. Tumour necrosis factor alpha, IL-6, and cortisol indicate the presence of an inflammatory process and, together with high tHcy, have been associated with neuronal loss.

Procedures for the collection of study measures

Participants recorded demographic information at the initial assessment, which also included cardiovascular history and testing with the MMSE. Consent regarding participants were then referred for an echocardiographic examination to determine their EF which we used, together with clinical history and review of medical notes, to allocate participants to the HF, IHD, and control groups. Participants returned for the 120 min face-to-face collection of outcomes within 2 weeks of completion of the echocardiogram. They donated a fasting blood sample between 8 and 9 am on the day of their cognitive assessment. These samples were processed immediately after venepuncture to extract plasma and serum, which were then batched and stored at \( 80^\circ \)C until assayed. Finally, we acquired the MRI scan images 2–8 weeks after the cognitive assessment.

Statistical methods

The data were managed and analysed with Stata version 11.2 (StataCorp, College Station, TX, USA). We used descriptive statistics to summarize data, cross-tabulation to determine their distribution according to group membership (Pearson’s chi-square statistic: \( \chi^2 \)), and analysis of variance (one-way analysis of variance or Kruskal–Wallis test) to compare the distribution of numerical variables. Initially, we analysed biochemical data as continuous variables, but later investigated their effect on outcomes according to quartiles (highest compared with all others) or, in the case of BNP and tHcy, according to the clinically established cut points 100 pg/mL and 13 \( \mu \)mol/L.

We used linear regression (regress command) to investigate the differences between IHD and HF participants and controls on the cognitive tests, taking into account the contribution of age, gender, education, and physical activity. These variables were part of the best fit explanatory model of cognitive function according to the cardiological group (they were all associated with P-values < 0.1). The selection of variables for the analysis of brain images followed the same principle. Initially, we investigated the contribution of all measured factors to total GM and selected the best parsimonious regression model that included, along with group membership, age, gender, and high tHcy. We also investigated the association between total GM volume and ejection fraction and the result on the 6 min walk test for patients with HF using Pearson correlation. Alpha was set at 5% and all statistical tests reported are two-tailed.

We used a full 2 x 2 factorial SPM design to model regional GM volume differences between the study groups, and included age (lower or greater/equal 70 years), gender, and tHcy grouping as co-variates. We declared as significant regional differences associated with a between group difference of at least 100 voxels and maximum P-value of 0.01.

The results of our pilot study showed that patients with HF and healthy controls had CAMCOG scores of 93.5 (standard deviation = 6.1, n = 31) and 99.9 (standard deviation = 2.4, n = 24). That study did not include a group with IHD, which we expected would have a cognitive performance that would fall between patients with HF and controls (mean of about 97, standard deviation of about 5). Such a difference could be declared as statistically significant with 53 participants in each group (80% power). As the recruitment of 53 eligible people with HF proved difficult within the timeframe of the project, we inflated the number of participants with IHD and controls to ensure that the study was sufficiently powered to declare such differences as significant (estimated power of at least 82%).

Results

One hundred and sixty-nine participants consented to complete all study assessments, but 14 had to be excluded from the analyses because of unusable brain images (distortions caused by movement = 9, scan artefacts = 3, brain tumour = 1). The remaining 155 participants consisted of 64 controls, 56 adults with IHD, and another 35 with HF. For 24 (68.6%) of the 35 people with HF, there was evidence that IHD was the most likely cause of their systolic dysfunction. The remainder 11 participants with HF had systolic dysfunction of uncertain aetiology. They were distributed as follows according to the NYHA Functional Classification: 5 (14.3%) Class III, 19 (54.3%) Class II, and 11 (31.4%) Class I. Table 1 summarizes their demographic, lifestyle, clinical, and laboratory characteristics. Adults with HF had lower scores than IHD and healthy controls on measures of memory and psychomotor speed, but not on the CAMCOG. We also found that participants with HF showed a relative loss of total GM compared with adults with IHD (crude analysis).

We then examined the cognitive scores of participants compared with non-cardiac controls and adjusted the analyses for the effect of confounding by age, gender, education, smoking, physical activity, and prevalent hypertension. Figure 1 summarizes the results of these analyses. Participants with IHD and HF had CAMCOG score 1.8 and 2.8 points lower than non-cardiac controls (P = 0.101 and P = 0.029, respectively). However, people with HF had significantly lower scores than healthy controls on measures of immediate recall, long delay recall, and digit code. Adults in the IHD group also had lower long delay recall scores than controls without IHD (P = 0.047). There were no other significant differences between groups. Of note, all non-cognitive variables listed in Table 1 were included in the regression models and we used a stepwise approach to remove one variable at a time until all remaining variables were associated with at least a 10% change in the adjusted R-squared and had a P-value < 0.1. In the case of the CAMCOG score, the variables retained in the model were age, gender, education, physical activity, and use of statins.

We investigated the association between measured factors and total brain GM (Figure 2) and included the relevant factors in the analysis of regional differences in the distribution of GM among participants with HF, IHD, and controls without IHD (2 x 2 pairwise comparisons). Figure 3 illustrates the results of these analyses. We also found that among participants with HF, total GM volume was not associated with performance on the 6 min walk test (Pearson \( r = 0.11, P = 0.537 \)) or ejection fraction (Pearson \( r = 0.04 \)) with a between group difference of at least 100 voxels and high tHcy, which have been associated with neur...
<table>
<thead>
<tr>
<th>Table 1</th>
<th>Demographic, lifestyle, clinical, and cognitive characteristics of adults without IHD or HF (controls), with IHD, and with HF who completed the imaging substudy</th>
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<tr>
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<td><strong>Controls (n = 64)</strong></td>
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<tr>
<td><strong>Demographics</strong></td>
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</tr>
<tr>
<td>Age, mean years ± SD</td>
<td>68.7 ± 11.3</td>
</tr>
<tr>
<td>Male gender, n (%)</td>
<td>22 (34.4)</td>
</tr>
<tr>
<td>Australia born, n (%)</td>
<td>37 (57.8)</td>
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<tr>
<td>Married, n (%)</td>
<td>50 (78.1)</td>
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<tr>
<td>Education, mean years ± SD</td>
<td>12.3 ± 2.9</td>
</tr>
<tr>
<td><strong>Lifestyle</strong></td>
<td></td>
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<tr>
<td>Ever smoker, n (%)</td>
<td>33 (51.6)</td>
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<tr>
<td>Current smoker, n (%)</td>
<td>5 (7.8)</td>
</tr>
<tr>
<td>Risk alcohol use, n (%)</td>
<td>14 (21.9)</td>
</tr>
<tr>
<td>Physically active, n (%)</td>
<td>13 (20.3)</td>
</tr>
<tr>
<td>BMI ≥ 25 kg/m², n (%)</td>
<td>41 (64.1)</td>
</tr>
<tr>
<td><strong>Clinical measures</strong></td>
<td></td>
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<tr>
<td>Use of a beta-blocker, n (%)</td>
<td>5 (7.8)</td>
</tr>
<tr>
<td>Use of a statin, n (%)</td>
<td>7 (10.9)</td>
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<tr>
<td>Ejection fraction, mean ± SD</td>
<td>68.1 ± 5.2</td>
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<tr>
<td>Six-minute walk, mean metres ± SD</td>
<td>465.6 ± 160.1</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>22 (34.4)</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>8 (12.5)</td>
</tr>
<tr>
<td>Dyslipidaemia, n (%)</td>
<td>25 (39.1)</td>
</tr>
<tr>
<td>HADS-D, median score (IQR)</td>
<td>2 (1–3)</td>
</tr>
<tr>
<td>HADS-A, median score (IQR)</td>
<td>3 (1–5)</td>
</tr>
<tr>
<td><strong>Biochemistry</strong></td>
<td></td>
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<tr>
<td>BNP, mean pg/mL ± SD</td>
<td>59.4 ± 70.5</td>
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<tr>
<td>TNF-α, mean pg/mL ± SD</td>
<td>1.3 ± 1.2</td>
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<tr>
<td>Cortisol, mean nmol/L ± SD</td>
<td>320.4 ± 94.7</td>
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<tr>
<td>IL-6, mean pg/mL ± SD</td>
<td>2.7 ± 4.8</td>
</tr>
<tr>
<td>tHcy, mean μmol/L ± SD</td>
<td>12.4 ± 3.5</td>
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<tr>
<td><strong>Cognitive measures</strong></td>
<td></td>
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<tr>
<td>IQ, mean score ± SD</td>
<td>113.8 ± 5.5</td>
</tr>
<tr>
<td>CAMCOG, mean score ± SD</td>
<td>94.7 ± 5.3</td>
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<tr>
<td>CVLT immediate recall, mean ± SD</td>
<td>48.6 ± 12.2</td>
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<tr>
<td>CVLT short delay, mean ± SD</td>
<td>9.8 ± 3.8</td>
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<tr>
<td>CVLT long delay, mean ± SD</td>
<td>10.4 ± 3.8</td>
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<tr>
<td>CVLT long cued recall, mean ± SD</td>
<td>11.1 ± 3.3</td>
</tr>
<tr>
<td>Digit coding, mean score ± SD</td>
<td>57.7 ± 16.0</td>
</tr>
<tr>
<td>Digit copy, mean score ± SD</td>
<td>94.0 ± 24.7</td>
</tr>
<tr>
<td><strong>Neuroimaging</strong></td>
<td></td>
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<tr>
<td>Total grey matter, mean mm³ ± SD</td>
<td>549.6 ± 51.4</td>
</tr>
</tbody>
</table>

*Two people with HF did not complete this task.
*Data missing for four controls and one person with IHD.
*One person with HF did not complete this task.

IHD, ischemic heart disease; HF, heart failure; IQ, intelligence quotient; HADS-D, Hospital Anxiety and Depression Scale—depression subscale; HADS-A, Hospital Anxiety and Depression Scale—anxiety subscale; IQR, interquartile range; BNP, B-type natriuretic peptide; TNF-α, tumour necrosis factor alpha; IL-6, interleukin-6; CAMCOG, Cambridge Cognitive Examination of the Elderly; CVLT, California Verbal Learning Test.
The use of statins or beta-blockers was not associated with the distribution of GM volume across the three study groups.

Compared with healthy controls, the brain regions of participants with HF that showed the greatest loss of GM included the left cingulate, the right inferior frontal gyrus, the left middle and...
superior frontal gyri, the right middle temporal lobe, the right and left anterior cingulate, the right middle frontal gyrus, the inferior and precentral frontal gyri, the right caudate, and occipital–parietal regions involving the left precuneus (Figure 3A and Supplementary material online, Table S1A). Compared with IHD controls, participants with HF showed evidence of loss of GM in the right middle temporal lobe, the right anterior cingulate and medial frontal lobe, the left lentiform nucleus and adjacent areas, the right precuneus, the right thalamus and lentiform nucleus, and other regions extending from right and left middle and superior frontal cortex (Figure 3B and Supplementary material online, Table S1B). The relative loss of GM among participants with HF compared with healthy controls was much less extensive, but affected overlapping regions such as the left medial frontal cortex, the left cingulate and precuneus, the left and right parahippocampal gyri, and the right and left middle temporal gyri (Figure 3C and Supplementary material online, Table S1C). There were no brain regions in which participants with HF had more GM than controls with or without IHD (data not shown). Similarly, there were no brain regions in which participants with IHD had more GM than healthy controls. Detailed results of the imaging analyses appear in Supplementary material online, Table S1.

**Discussion**

The results of this study show that adults with HF have worse immediate and long-term memory and psychomotor speed than healthy controls. We also found that participants with HF display a relative loss of cerebral GM in various cortical and subcortical regions extending to the frontal lobes, anterior cingulate, and temporal–parietal lobes. Contrary to expectations, our results showed no evidence of cognitive deficits in people with HF compared with IHD. However, we found a relative loss of regional GM among participants with HF compared with IHD that was less extensive but had a similar topographic distribution when the former were compared with healthy controls (which suggests that these changes may be relatively specific to HF).

Previous studies had already reported that people with HF have worse cognitive function than healthy controls, but it was unclear if those deficits were due to confounding. As far as we are aware, this is the first study that included an additional IHD control group that shares common risk factors with HF, which allowed us to show that the cognitive losses may be a non-specific consequence of increasing cardiovascular disease burden. Moreover, our analyses revealed that these subtle deficits (only around 0.5 SD lower than controls and thus unlikely to be associated with overt clinical impairment) cannot be explained by impaired left ventricular ejection fraction, prevalent comorbid conditions, or biochemical markers.

The acquisition of structural brain images allowed us to examine the impact of both HF and IHD on cerebral GM and to show that people with HF display more widespread and extensive brain changes than adults with IHD. Another imaging study that investigated cerebral blood flow in 17 people with HF found that the posterior cingulate and precuneus were the brain regions that showed the greatest reduction in blood flow compared with 18 controls. The posterior association cortex plays an important role in the successful retrieval of memory traces, and the precuneus, posterior cingulate, and retrosplenial cortex have major bidirectional connections with the medial temporal lobes in primates. In addition,
loss of GM density in subcortical structures and frontal cortex may contribute to compromise attention, memory, and executive functions, and existing evidence suggests that the anterior cingulate and areas of the lateral and medial frontal cortex work in tandem during activities that demand mental effort, such as in tasks that require attention, mental associations, and strategic thinking. The outcomes of our study are consistent with these observations, and may be interpreted as indicating that HF, and to a lesser extent IHD, undermines the performance of participants on tasks that are mentally demanding.

Our imaging findings have also shown that high tHcy makes an independent contribution to the relative loss of cerebral GM observed among participants with HF and IHD. High tHcy has been associated with cognitive decline and brain atrophy, and recent evidence suggests that lowering tHcy may decrease the rate of neuronal loss, possibly because apoptosis and vascular pathology are attenuated by consumption of folate and vitamin B12. Our results also suggest that male gender and older age increase loss of GM. Data from community samples of older adults have demonstrated that increasing age is directly associated with the loss of cerebral GM, but there is no evidence that men and women would be differentially affected.

Limitations
The study sample consisted of a group of motivated volunteers with and without IHD or with HF. As people who volunteer to take part in studies are commonly healthier than non-participants, healthy participant bias seems likely. This would have resulted in a bias that minimizes the differences between participants and would have moved our findings towards the null hypothesis. Hence, the deficits and changes that we did find are probably an underestimation of the differences that exist between these groups. In addition, our HF sample included only people with systolic dysfunction, and it is unclear whether these results can be extended to patients with HF due to non-systolic dysfunction. We also acknowledge that our study groups were not perfectly balanced for gender, HADS scores, and clinical measures such as hypertension and dyslipidaemia, although differences between groups were not marked and the analyses accounted for possible confounding. Furthermore, the inclusion of relatively young participants in the study may have contributed to attenuate the negative consequences of cardiac disease on cognitive function (which might be more pronounced in older people), although we found no obvious interaction between age and cardiac illness on cognitive scores. Another limitation is that, due to imaging artefacts, we did not examine differences in the distribution of GM in the left temporal lobe. The cross-sectional nature of our data preclude definitive conclusions as to whether HF, and to a lesser extent IHD, is causally related to cognitive decline and loss of cerebral GM. Moreover, the assessment of cognitive function was not blinded to the clinical status of participants, although imaging and biochemical procedures were. It is possible that such a non-blinding could have biased the results of our structured cognitive assessments. Finally, we did not record the duration of HF symptoms or of IHD because we were not confident that such information would be accurate and reliable, and are, consequently, unable to comment whether longer illness duration would have been associated with greater impairment of cognitive function or GM loss. These questions would have been more adequately addressed by a longitudinal study.

Conclusion
In summary, our study shows that people with HF experience loss of GM in brain regions that are relevant to cognitive function and that compromise performance on cognitive tasks that require mental effort. Importantly, our results are consistent with the observation that people with HF have trouble adhering to complex self-care advice, and suggest that simpler approaches to self-management may be required. Future studies should aim to clarify the physiological pathways that link HF to loss of cerebral GM and cognitive impairment, and longitudinal surveys should determine whether the observed cerebral and cognitive changes are progressive in nature.

Role of authors
O.P.A., N.T.L., L.A., and L.F. conceived and designed the study, and obtained funding. O.P.A., N.T.L., L.A., L.F., and C.B. assisted with recruitment and data collection. O.P.A. and G.J.G. analysed the data and all authors contributed to the interpretation of the results. O.P.A. drafted the manuscript. All authors reviewed the manuscript critically and approved its submission for publication.

Supplementary material
Supplementary material is available at European Heart Journal online.

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Conflict of interest: the authors declare that they have no conflict of interest.

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