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Association between major depressive symptoms in heart failure and impaired regional cerebral blood flow in the medial temporal region: a study using ^{99m}Tc-HMPAO single photon emission computerized tomography (SPECT)

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ABSTRACT

Background and purpose. Depressive symptoms are frequently associated with heart failure (HF), but the brain mechanisms underlying such association are unclear. We hypothesized that the presence of major depressive disorder (MDD) emerging after the onset of HF would be associated with regional cerebral blood flow (rCBF) abnormalities in medial temporal regions previously implicated in primary MDD, namely the hippocampus and parahippocampal gyrus.

Method. Using ^{99m}Tc-SPECT, we measured rCBF in 17 elderly MDD-HF patients, 17 non-depressed HF patients, and 18 healthy controls, matched for demographic variables. Group differences were investigated with Statistical Parametric Mapping.

Results. Significant rCBF reductions in MDD-HF patients relative to both non-depressed HF patients and healthy controls were detected in the left anterior parahippocampal gyrus and hippocampus (ANOVA, $p = 0{\cdot}008$ corrected for multiple comparisons) and the right posterior hippocampus and parahippocampal gyrus ($p = 0{\cdot}005$ corrected). In the overall HF group, there was a negative correlation between the severity of depressive symptoms and rCBF in the right posterior hippocampal/parahippocampal region ($p = 0{\cdot}045$ corrected).

Conclusions. These findings are consistent with the notion that the medial temporal region is vulnerable to brain perfusion deficits associated with HF, and provide evidence that such functional deficits may be specifically implicated in the pathophysiology of MDD associated with HF.

INTRODUCTION

Symptoms of major depressive disorder (MDD) emerge frequently in elderly subjects after the onset of heart failure (HF) (Freedland *et al.* 2003; Thomas *et al.* 2003). Together with cognitive deficits, the presence of major depressive symptoms in HF is associated with longer

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hospitalization periods and increased death rates (Jiang *et al.* 2001; Braunstein *et al.* 2003). The impact of MDD on the prognosis of HF, including its influence on mortality, is independent both from the severity of the cardiac symptoms, and from the deficiency in cardiac output as measured by the left ventricular ejection fraction (LVEF) (Junger *et al.* 2005).

The brain mechanisms underlying the association between MDD and HF remain to be clarified. Several functional imaging studies using single photon emission computerized tomography (SPECT) have reported global cerebral blood flow (CBF) reductions in HF patients in comparison to healthy control subjects (Rajagopalan *et al.* 1984; Kamishirado *et al.* 1997; Georgiadis *et al.* 2000; Gruhn *et al.* 2001). Such chronic CBF reductions have been proposed to mediate the cognitive deficits and localized neurological symptoms commonly associated with HF (Ackerman, 2001; Gruhn *et al.* 2001), and they could also contribute to the emergence of major depressive symptoms in HF (Doraiswamy *et al.* 1999). However, the latter possibility could not be investigated in those previous SPECT reports, as there was no objective assessment of depressive symptoms in the HF subjects studied.

Recent experimental models of brain hypoperfusion in animals suggest that the hippocampus, periventricular white matter and basal ganglia, are particularly vulnerable to the damaging effects of chronic CBF reductions (Farkas *et al.* 2000, 2002). The findings regarding the hippocampus could be especially relevant to the pathophysiology of the co-morbidity between MDD and HF, as this region takes part in the ventral limbic network thought to be critical to the mediation of both normal sadness and the symptoms of MDD (Mayberg *et al.* 1999). Functional activity changes and volumetric reductions of the hippocampus and other medial temporal structures have often been reported in subjects with primary MDD compared to healthy controls (Drevets *et al.* 2002; Campbell *et al.* 2004; Neumeister *et al.* 2005), although these findings have not always been replicated and may be influenced by antidepressant use (Vythilingam *et al.* 2004) and length of illness (Sheline, 2003). There have also been findings of depressive symptoms emerging in stroke patients with ischemic lesions involving temporo-limbic structures (Dam, 2001; Vataja *et al.* 2001, 2004). Such evidence suggests that localized functional deficits in the medial temporal region, secondary to chronic brain perfusion abnormalities, could underlie the emergence of MDD in HF subjects.

Brain perfusion abnormalities in the hippocampus and other medial temporal structures could not be investigated accurately in the functional imaging studies of HF reviewed above, due both to the low spatial resolution of the techniques employed, and the use of quantification methods involving the manual placement of large-sized regions of interest (ROIs) on selected brain portions (Doraiswamy *et al.* 1999; Gruhn *et al.* 2001). In the present study, we investigated the presence of regional CBF (rCBF) deficits in 17 elderly patients with HF and MDD compared to 17 non-depressed HF subjects and 18 age-matched healthy controls, using high-resolution SPECT with technetium-99m-hexamethylpropylene-amine-oxime (^{99m}Tc-HMPAO) as perfusion tracer. The patterns of rCBF deficits were investigated on a voxel × voxel basis, using Statistical Parametric Mapping (SPM2) (Friston *et al.* 1996). We hypothesized that, in comparison to the other two groups, HF subjects with co-morbid MDD would show significant perfusion deficits in the medial temporal region. We also predicted that in the overall HF sample, there would be significant correlations between the severity of depressive symptoms and rCBF measurements in the medial temporal region. In addition, as it has been previously suggested that MDD associated with signs of cerebrovascular disease may be less responsive to pharmacological treatment (Taylor *et al.* 2003; Baldwin *et al.* 2004), we wished to investigate whether the degree of medial temporal rCBF deficits in the HF-MDD group would predict poorer response to the standardized antidepressant treatment offered to those subjects after the initial SPECT evaluation. Finally, the use of the voxel-based quantification approach allowed us to investigate, on an exploratory basis, whether the co-morbidity between HF and MDD would be associated with the presence of significant rCBF deficits in other brain regions.

Table 1. *Demographic and clinical characteristics of subjects with heart failure and healthy controls*

	MDD-HF ($n=17$)	Non-depressed HF ($n=17$)	Controls ($n=18$)	p value (between the three groups)	p value (between the two HF groups)
Mean age (yr) ($\pm$S.D.)	76·0$\pm$6·4	73·7$\pm$5·4	72·8$\pm$4·8	0·226[c]	0·204[b]
Gender (male/female)	8/9	9/8	6/12	0·486[a]	0·724[a]
Mean years of education ($\pm$S.D.)	4·0$\pm$2·5	5·4$\pm$3·6	5·7$\pm$2·7	0·203[c]	0·218[b]
Cerebral dominance (right/non-right)	15/2	17/0	17/1		0·145[a]
Social class (A/B/C)	1/8/8	4/7/6	3/10/5	0·553[a]	0·341[a]
Previous history of hypertension	15	17	10	0·002[a]	0·145[a]
Mean LVEF ($\pm$S.D.)	35·5$\pm$7·6	39·8$\pm$3·3	73·4$\pm$4·2	$<$0·001[c]	0·119[b]
Functional class NYHA (II/III)	8/9	10/7		$<$0·001[a]	0·492[a]
History of atrial fibrillation	3	2	0	0·195[a]	0·628[a]
History of cigarette smoking	4	4	4	0·994[a]	1·00[a]
History of diabetes	7	7	6	0·858[a]	1·00[a]

S.D., Standard deviation; MDD-HF, major depression associated with heart failure; HF, heart failure; LVEF, left ventricle ejection fraction; NYHA, New York Heart Association classification for heart failure.
[a] χ^2 test; [b] unpaired t test; [c] ANOVA.

MATERIALS AND METHOD

Subjects and assessment schedules

Local ethics committees approved the study and written informed consent was obtained from all subjects after a complete description of the study.

We investigated 17 elderly HF patients who developed MDD symptoms (mean age = 76·00$\pm$6·42 years) and 17 non-depressed HF patients (mean age = 73·77$\pm$5·43 years), using a cross-sectional design. The MDD group had HF due to either dilated cardiomyopathy ($n=8$) or ischemic heart disease ($n=9$). They were all in New York Heart Association (NYHA) functional classes II ($n=8$) or III ($n=9$). The diagnosis of HF preceded the emergence of depressive symptoms in all of those subjects, and none of them had been previously exposed to antidepressant drugs. The non-depressed HF patients were also in NYHA functional classes II ($n=10$) or III ($n=7$), and included eight subjects with HF due to dilated cardiomyopathy and nine patients with ischemic heart disease. None of the non-depressed HF subjects had a previous history of major depressive episodes. Patients in the two groups presented with chronic symptoms of HF, and had been stable on an optimized cardiologic medication regimen for at least 1 month prior to the study. The presence of HF was determined by detailed cardiological anamnesis, physical examination, electrocardiogram and echocardiography LVEF below 50%. The pharmacological treatment for both HF groups included the use of angiotensin converting-enzyme inhibitors (ACEI) ($n=31$), β-blockers ($n=12$), diuretics ($n=10$) and statins ($n=2$). In addition, nine depressed and four non-depressed HF patients were on regular aspirin use ($p=0·157$, df = 1, χ^2 test). Five HF subjects were also receiving digoxin, and anticoagulant therapy for the treatment of atrial fibrillation, and 14 patients were taking oral anti-diabetic agents. The HF subjects with concomitant hypertension ($n=32$) were treated with the same drugs as indicated above for HF symptoms. Patients with a history of myocardial infarction within the past 3 months or hospitalization for cardiovascular disease within the past month were excluded from both HF groups. A summary of their demographic and clinical characteristics is given in Table 1.

The presence or absence of co-morbid MDD in HF subjects was assessed according to DSM-IV criteria (APA, 1994), based on information obtained with the Structured Clinical Interview for DSM-IV – Patient Edition (SCID-I/P; First *et al.* 1993). The severity of depressive symptoms in both HF groups was assessed using the 31-item Hamilton Rating Scale for Depression (HDRS; Hamilton, 1980).

The healthy comparison group ($n=18$; mean age = 72·78$\pm$4·75 years) had no symptoms suggestive of HF or psychiatric/neurological disorders based on general medical questioning,

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physical and neurological examination, and interviewing using the SCID-I/P. Ten control subjects were under pharmacological treatment for hypertension at the time of the experiment, with β-blockers ($n=1$), ACEI ($n=6$) or diuretics ($n=3$). Six subjects were taking oral anti-diabetic agents, and one was taking aspirin. The HF and healthy control groups were not significantly different in terms of demographic characteristics (Table 1). Both HF groups (depressed and non-depressed) showed significantly lower mean LVEF relative to healthy controls ($35{\cdot}5 \pm 7{\cdot}3$, $39{\cdot}8 \pm 3{\cdot}3$ and $73{\cdot}4 \pm 4{\cdot}2$ respectively) ($F=166{\cdot}02$, df$=2$, 49, $p<0{\cdot}001$, ANOVA). There were no differences between the three groups in terms of history of smoking or diabetes (Table 1).

Subjects in the three groups were free from psychoactive drugs including benzodiazepines, mood stabilizers and antidepressants. Also, subjects with a history of hypo- or hyperthyroidism, lung or liver disease were excluded from the three groups. Other exclusion criteria for all groups were: presence of signs of carotid obstruction at physical examination; presence of structural neuroimaging signs of cerebrovascular infarcts; personal or first-degree family history of neurodegenerative disorders; and family history of other major psychiatric conditions including MDD, as assessed using the SCID-I/P for DSM-IV.

A cognitive test battery was conducted within 1 week prior to SPECT scanning in all groups, using the Mini-Mental State Examination (MMSE; Folstein *et al.* 1983), and the section for assessment of cognitive function from the Cambridge Mental Disorders of the Elderly Examination (CAMCOG; Roth *et al.* 1986).

After the initial clinical and brain imaging evaluation, the HF patients with MDD were treated with selective serotonin reuptake inhibitor (SSRI) antidepressant drugs (citalopram in 13 cases, mean dose $=36{\cdot}36 \pm 8{\cdot}09$ and sertraline in four cases, mean dose $=75{\cdot}00 \pm 28{\cdot}86$), and re-evaluated blindly by one of the authors (R.M.S.T) with the HDRS at 3 and 8 weeks. Treatment response was assessed as the percentage of HDRS change by the end of 8 weeks; subjects were classified as treatment responders (when there was at least a 50% decrease in HDRS scores), partial responders (20–50% HDRS change), or non-responders (HDRS change $<20\%$).

Imaging data acquisition

SPECT images were acquired after intravenous injection of 30 mCi ^{99m}Tc-HMPAO at rest (eyes closed and ears plugged). A dual-headed SPECT camera (Sophy DST-SMV/General Electric, Buc Cedex, France) equipped with high-resolution collimators (resolution 7·7 mm at 10 cm) was used. Complete 360° samplings of 128 projections were acquired on 128×128 matrices (30 s per view; total scanning time 35 min). Images were reconstructed using the iterative Ordered Subset Expectation Maximization method (8 subsets and 2 iterations), after Metz pre-filtering (psf FWHM $=4$ pixels and order $=8$), with all projections corrected for scattering (secondary window subtraction with factor 0·5). Attenuation correction was performed using the Chang method (uniform linear attenuation coefficient $=0{\cdot}159\ \mathrm{cm}^{-1}$), applied on reconstructed, 12-mm-thick transaxial slices. Given the clear transition of activity levels between bone tissue and the cerebral cortex obtained after ^{99m}Tc-HMPAO injection, the body edge was manually defined for attenuation correction for each brain slice in all subjects, using the program MRIcro (C. Rorden, University of Nottingham, UK).

In addition to SPECT scanning, a structural brain scan was acquired in all subjects in the three groups. These images were inspected by an experienced radiologist (C.C.C) who was blinded to diagnostic status, in order to allow the exclusion of subjects with signs of cortical infarctions or other gross brain lesions. In 10 MDD-HF patients, seven non-depressed HF patients and two healthy controls, computed tomography (CT) scans were obtained. In the remaining subjects, magnetic resonance imaging (MRI) data were acquired, using a 1.5 T GE Signa LX-Cvi scanner (Milwaukee, WI, USA). For the subjects who were examined with MRI, semi-quantitative ratings for white-matter hyperintensities (WMH) (Scheltens *et al.* 1993) were compared between MDD-HF patients, non-depressed HF patients and healthy controls. This analysis, reported elsewhere, showed no differences in WMH ratings between groups, although a significant direct correlation was detected between the severity of frontal

periventricular WMH and HDRS ratings in the MDD-HF group (Almeida *et al*. 2005). Finally, we did not exclude any subjects with signs of dilated lateral ventricles, which were noticeable in mild to moderate degrees at visual inspection in a greater proportion of subjects with HF relative to the control group. However, two subjects in the MDD-HF group and one control subject were judged as showing a considerable overall enlargement of cerebrospinal fluid (CSF) spaces; given that SPM analyses of functional imaging data may be subject to artifacts due to structural brain variations (Gispert *et al*. 2003), we repeated the entire SPECT image processing protocol and voxel-based statistical analyses after the exclusion of those three subjects.

SPECT image processing

SPECT image analysis was performed using the SPM program (Friston *et al*. 1996), version 2000 (SPM2). A customized SPECT template was created specifically for the study, consisting of a mean image of all healthy controls and HF subjects. This strategy was aimed to match the template more closely to the population under investigation and the image acquisition protocols used (Gispert *et al*. 2003). Initially, images were spatially normalized to the standard SPM SPECT template, based on the Montreal Neurological Institute (MNI) template (Mazziotta, 1994). Such a spatial normalization step was restricted to linear 12-parameter affine transformations, in order to minimize deformations of the original images. Subsequently, images were smoothed with an isotropic Gaussian kernel (12 mm FWHM), and averaged to provide the mean SPECT image in stereotactic MNI space.

The processing of the original images from all HF patients and controls was then carried out, beginning by spatial normalization of images using our study-specific SPECT template, with 12-parameter linear as well as nonlinear ($3 \times 4 \times 3$ basis functions) transformations. Spatially normalized images were then re-sliced using tri-linear interpolation to a final voxel size of $2 \times 2 \times 2$ mm^3, and smoothed using a 12-mm Gaussian kernel.

Statistical analysis

In order to investigate the presence of significant rCBF differences between the three groups, an overall analysis of variance (ANOVA) was initially carried out. Resulting statistics were thresholded at the one-tailed $p < 0{\cdot}01$ level of significance ($Z > 2{\cdot}33$), and displayed on a statistical parametric map (SPM) into standard anatomical space. In order to account for inter-individual differences in global CBF, the regional ^{99m}Tc-HMPAO uptakes were standardized to the mean global uptake using proportional scaling. This allowed the investigation of between-group differences in regional tracer uptake, avoiding the confounding influence of global CBF reductions. Only voxels with signal intensities above 50% of the mean global value were considered for such between-group comparison, in order to restrict the analysis to gray matter regions. First, the ANOVA map was searched for the presence of significant F values on the voxels contained in the hippocampus and parahippocampal gyrus, where rCBF abnormalities had been predicted *a priori*. The voxels mapped to these medial temporal structures were circumscribed using the small volume correction (SVC) tool available in the SPM package, whereby we applied predefined, spatially normalized volumes of interest on the ANOVA map (resulting in a search volume of 946 voxels for the hippocampus in each hemisphere, and 978 voxels for the parahippocampal gyrus). Any rCBF differences within those medial temporal areas were reported as significant if surviving family-wise error (FWE) correction for multiple comparisons ($p < 0{\cdot}05$) (Friston *et al*. 1996). *Post-hoc* evaluation of significant ANOVA findings in these regions was then performed with secondary two-tailed independent sample t tests.

Subsequently, the ANOVA map was inspected again, in order to identify significant between-group rCBF differences in other, unpredicted regions across the entire brain. Findings in these additional areas would only be reported as significant if surviving FWE correction for multiple comparisons over the whole brain (search volume of approximately 245 000 voxels).

Finally, linear correlations between regional tracer uptake values and initial HDRS scores and total CAMCOG scores were calculated for the entire HF group. This analysis was first performed for the medial temporal region using the SVC tool mentioned previously, and

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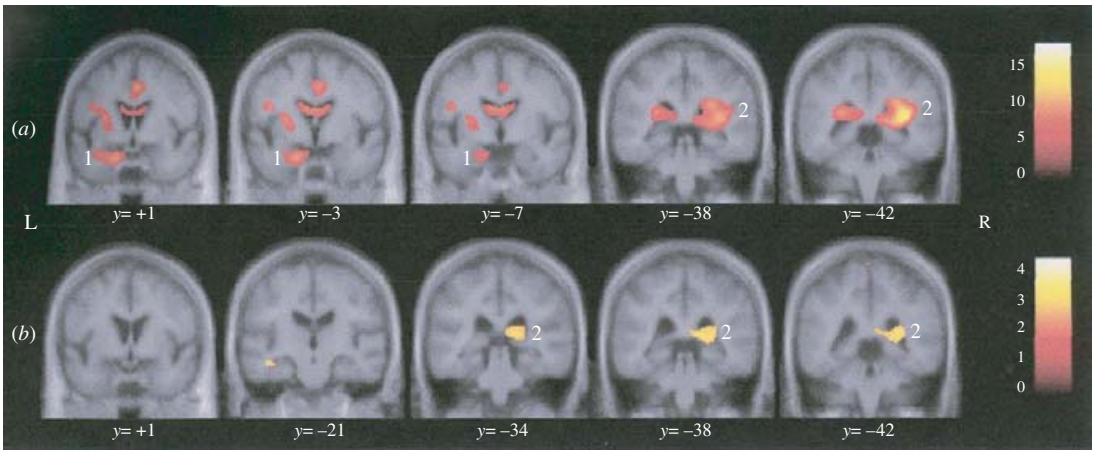

FIG. 1. (*a*) Statistical parametric map showing rCBF differences (ANOVA) between patients with major depressive disorder and heart failure (MDD-HF), non-depressed HF patients and healthy controls, at the $Z > 2{\cdot}55$ cut-off (corresponding to $p < 0{\cdot}005$, uncorrected for multiple comparisons). Significant findings have been overlaid on coronal sections of a mean structural MRI image of 33 subjects from our sample, spatially normalized (linear transformations only) to the T_1-weighted Montreal Neurological Institute template available in the SPM2 package. The numbers associated with each frame represent standard coordinates in the *y* axis. Two voxel clusters are shown on the medial temporal regions where tracer uptake differences had been predicted *a priori*, involving respectively: the left anterior parahippocampal gyrus and hippocampus (labelled with the white-printed number 1) and the right posterior hippocampus and parahippocampal gyrus (labelled with number 2). Both clusters remained significant after family-wise error (FWE) correction for multiple comparisons ($p < 0{\cdot}05$) (small volume correction over medial temporal structures). *Post- hoc* unpaired *t* tests showed that tracer uptake values in those clusters were significantly reduced in the HF-MDD group relative either to the non-depressed HF group or the healthy control group (see Table 2). Additional, unpredicted foci of between-group rCBF differences are seen on other cortical areas, but these did not retain significance after FWE correction for multiple comparisons over the whole brain. (*b*) Foci of negative linear correlations between Hamilton Rating Scale for Depression scores and rCBF indices in the overall HF group are shown at the $Z > 2{\cdot}55$ cut-off. One cluster of statistical significance (labelled with number 2) ($p < 0{\cdot}05$, FWE corrected for multiple comparisons) is seen on the same right medial temporal region where rCBF reductions were detected in MDD-HF patients relative to the two other groups. Abbreviations: L, left; R, right.

subsequently for the entire brain. Significant findings in those correlational analyses were reported at the $p < 0{\cdot}05$ level corrected for multiple comparisons (FWE). The investigation of correlations was repeated in the MDD-HF group using the percentage of HDRS score change after pharmacological treatment.

In all analyses, we converted MNI coordinates of voxels of maximal statistical significance to the Talairach & Tournoux (1988) system (Brett *et al*. 2002).

RESULTS

Between-group rCBF comparisons

The ANOVA map comparing rCBF patterns between the three groups indicated the presence of two voxel clusters of statistical significance involving the medial temporal regions where tracer uptake differences had been predicted *a priori* (Fig. 1*a*). These were located, respectively in: the left anterior parahippocampal gyrus [Brodmann areas (BA) 28/34/35/36] and anterior hippocampus ($p = 0{\cdot}008$, FWE corrected for multiple comparisons); and the right posterior hippocampus and posterior parahippocampal gyrus (BA27/30) ($p = 0{\cdot}005$, corrected) (Table 2). *Post-hoc* unpaired *t* tests showed that tracer uptake values in the HF-MDD group were significantly reduced relative to either the non-depressed HF group or healthy controls, both for the left anterior medial temporal region (peak *t* test value = 3·16, df = 32, $p = 0{\cdot}001$; and $t = 4{\cdot}66$, df = 33, $p < 0{\cdot}001$ respectively); and the right posterior medial temporal region ($t = 3{\cdot}45$, df = 32, $p = 0{\cdot}001$; and $t = 4{\cdot}28$, df = 33, $p < 0{\cdot}001$ respectively).

As seen in Fig. 1*a*, the cluster of between-group tracer uptake difference involving the right posterior medial temporal region also encompassed a substantial number of voxels located in the adjacent lateral ventricle. Thus, it is possible that this finding could have been confounded by ventricle size differences between

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Table 2. *Significant regional cerebral blood flow reductions in heart failure (HF) patients with co-morbid major depressive disorder (MDD) relative to non-depressed HF patients and healthy controls and correlations with depression severity scores*

	Statistical test value	*p* value (corrected)[a]	Size of cluster[b]	Coordinates in mm (x, y, z)[c]	MDD-HF < non-depressed HF: peak *Z* score[d]	MDD-HF < healthy controls: peak *Z* score[e]
Regions showing between-group rCBF differences						
Right posterior hippocampus/ posterior parahippocampal gyrus (BA27/30)	11·80[f]	0·005	112	26, −42, 3	3·24	4·28
Left anterior parahippocampal gyrus (BA28/34/35/36)/anterior hippocampus	10·98[g]	0·008	239	−15, −1, −23	3·00	4·22
Regions showing negative correlations between rCBF and HDRS scores						
Right posterior hippocampus/posterior parahippocampal gyrus (BA27/30)	3·06[b]	0·045	101	24, −38, 8	n.a	n.a

MDD-HF, Major depression associated with heart failure; HF, heart failure; rCBF, regional cerebral blood flow; HDRS, Hamilton Depressive Rating Scale; n.a., not applicable.

[a] Statistical significance after correction for multiple comparisons; inferences were made at the level of individual voxels (family-wise error correction) (Friston *et al.* 1996). [b] Number of contiguous voxels that surpassed the initial threshold of $p<0{\cdot}01$ (uncorrected) in the statistical parametric maps. [c] Talairach & Tournoux (1988) coordinates of the voxel of maximal statistical significance within each cluster. [d] *Z* scores for the voxel of maximal statistical significance in the *post-hoc* comparison between depressed HF patients and non-depressed HF subjects (two-tailed *t* tests). [e] *Z* scores for the voxel of maximal statistical significance in the *post-hoc* comparison between depressed HF patients and healthy controls (two-tailed *t* tests). [f] *F* value (ANOVA comparison between the three groups) for the voxel of maximal statistical significance within each cluster. [g] *Z* score (linear correlation between the two variables) for the voxel of maximal statistical significance within the cluster.

the groups, particularly if its significant voxels had been located at coordinates equal to or closer than 12 mm to the border of the lateral ventricle (corresponding to the size of the Gaussian filter employed for image smoothing). In order to discard this possibility, we listed the coordinates of all voxels in the cluster showing rCBF differences in the right posterior medial temporal region at a stricter statistical threshold of $p<0{\cdot}001$ (corresponding to *Z* values $\geqslant 3{\cdot}09$). This coordinate listing indicated that there were 27 voxels mapped to the right posterior parahippocampal or hippocampal gray matter with coordinates located at distances greater than 12 mm from the border of the lateral ventricle, all of which had *Z* values $\geqslant 3{\cdot}09$. Moreover, when we repeated the between-group comparisons excluding the two MDD-HF patients and the healthy control subject who presented a considerable enlargement of CSF spaces, a similar pattern of between-group rCBF differences emerged, with tracer uptake reductions in the MDD-HF group relative to the two other groups detected again on the left anterior parahippocampal gyrus/hippocampus ($F=11{\cdot}42$, $p=0{\cdot}007$ corrected), and on the right posterior hippocampus/parahippocampal gyrus ($F=9{\cdot}06$, $p=0{\cdot}027$ corrected).

There were additional, unpredicted foci of between-group rCBF differences shown on the ANOVA map (Fig. 1*a*), but none of these attained statistical significance after correction for multiple comparisons over the whole brain ($p<0{\cdot}05$).

Depressive and cognitive rating scores and correlations with rCBF indices

As expected, the MDD-HF group had significantly higher mean scores on the HDRS than non-depressed HF patients and healthy controls ($27{\cdot}9\pm7{\cdot}6$, $7{\cdot}2\pm5{\cdot}3$, and $3{\cdot}3\pm1{\cdot}9$ respectively; $F=110{\cdot}52$, df = 2, 49, $p<0{\cdot}001$, ANOVA). In the MDD-HF group, the mean duration of the current major depressive episode was $8{\cdot}1\pm6{\cdot}7$ months, and this group also had a history of $1{\cdot}6\pm0{\cdot}6$ previous untreated episodes of major depression (all after the onset of HF), based on information obtained with the SCID-I/P.

There were significant differences between both HF groups (with and without MDD) and

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healthy controls on: mean MMSE scores (25·2 ± 2·2, 26·6 ± 3·1, 29·0 ± 1·8 respectively; $F = 11{\cdot}31$; df = 2, 49, $p < 0{\cdot}001$, ANOVA); total CAMCOG scores (52·4 ± 10·9, 70·2 ± 12·3, 83·2 ± 3·6 respectively; $F = 44{\cdot}52$, df = 2, 49, $p < 0{\cdot}001$, ANOVA); and on all CAMCOG subscales ($F > 4{\cdot}66$, df = 2, 49, $p < 0{\cdot}014$, ANOVA), with the exception of orientation subscores ($F = 2{\cdot}504$, df = 2, 49, $p = 0{\cdot}092$, ANOVA). *Post-hoc* comparisons showed lower CAMCOG subscores scores in the MDD-HF group compared to healthy controls in the subscales for orientation, language (comprehension and expression), attention, praxis, memory (recent and remote), calculation, abstract reasoning and perception (as tested with independent sample t tests; df = 33, $t > -2{\cdot}27$, $p < 0{\cdot}030$). The MDD-HF group had also lower scores relative to non-depressed HF subjects on the CAMCOG language, remote memory, praxis, calculation, abstract reasoning and perception subscales ($t > -2{\cdot}39$, df = 32, $p < 0{\cdot}023$).

The investigation of linear correlations between rCBF measurements and pre-treatment HDRS scores in the total sample of HF subjects showed significant negative correlations located at the same right posterior hippocampal and parahippocampal region where between-group tracer uptake differences had been found (see Fig. 1*b* and Table 2). There were no significant correlations between total CAMCOG scores and rCBF values in the medial temporal region in HF subjects.

Treatment response and rCBF indices

In our sample of HF patients with co-morbid MDD, there was a considerable reduction in HDRS scores both after 3 weeks (mean HDRS reduction = 45·47 ± 24·38 %) and after 8 weeks (mean HDRS reduction = 67·73 ± 25·23 %) of treatment with SSRI antidepressants. Two HF patients could not be re-evaluated after 8 weeks as they died from complication of their cardiac condition. From the remaining patients completing the clinical trial, 12 were considered treatment-responders, two were partial responders, and one was classified as non-responder. There were no significant correlations between percent changes in HDRS scores at either 3 or 8 weeks of treatment, and rCBF values in the medial temporal region or other brain areas in the MDD-HF group.

DISCUSSION

To the best of our knowledge, this is the first functional imaging study that investigated the presence of regional brain perfusion abnormalities in elderly HF subjects who developed MDD symptoms, compared to non-depressed HF patients and a healthy control group. The results obtained confirmed our prediction that significant rCBF deficits in the medial temporal region would be present in elderly HF subjects with co-morbid MDD.

The finding that the co-morbidity between MDD and HF is associated with reduced rCBF in the medial temporal region is consistent with previous functional and structural imaging studies that have highlighted medial temporal structures, such as the hippocampus and amygdala, among the preferential sites for the presence of brain abnormalities in patients with primary MDD (Drevets *et al.* 2002; Phillips *et al.* 2003; Campbell *et al.* 2004). Based on the results of the present study, we propose that chronic reductions in cardiac output associated with HF lead to altered functioning of temporo-limbic regions relevant to the regulation of mood, increasing the likelihood of incidence of depressive symptoms.

As the two HF groups did not differ in aspects related to their cardiac condition, it is possible that other causal influences, such as genetic factors or chronic stress, could have also contributed to the emergence of medial temporal lobe rCBF deficits only in HF-MDD subjects (Fuchs & Flugge, 2003). However, it is unlikely that genetic factors related to depression vulnerability would have influenced our rCBF results, as our HF patients with co-morbid MDD patients had no first-degree family history of mood disorders (van den Berg *et al.* 2001). Also, although it is known that temporo-limbic structures are susceptible to the effects of depression-related chronic hypercortisolism and stress (Vythilingam *et al.* 2004), the latter factors would be expected to be associated with an earlier age of onset of major depressive symptoms (van den Berg *et al.* 2001). Differently, our HF sample included only subjects with late-onset MDD, whose cardiological symptoms have preceded the emergence of depressive features. Furthermore, the influence of chronic stress on limbic rCBF patterns may have been

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minimized in our study by the use of the stress-modifying agent aspirin (Bednar & Gross, 1999) in a substantial proportion of the HF subjects, as well as the absence of significant differences in the exposure to this anti-inflammatory drug between the HF-MDD and non-depressed HF groups.

One other possibility is that rCBF patterns in the MDD-HF group in our study were influenced by the presence of gross cerebrovascular changes in these patients. It has been argued that the prominence of cognitive deficits seen in association with late-onset MDD would indicate the presence of neurodegenerative processes in such a subtype of depression (Hickie *et al*. 2001; Baldwin *et al*. 2004). There is abundant evidence that such degenerative pathology manifests itself as vascular-related neuroanatomical changes, either as gray matter infarcts or WMH (Taylor *et al*. 2003). However, in our study, it is unlikely that the perfusion abnormalities seen in the HF-MDD group were related to the presence of infarcts in the medial temporal lobe or other brain structures, as we excluded HF cases in which there were obvious signs of gross cerebrovascular changes in any gray-matter regions. On the other hand, assessments of WMH in the subsample of our subjects that were examined with MRI showed a significant direct correlation between the severity of frontal periventricular WMH and HDRS scores in the HF-MDD group (Almeida *et al*. 2005). These preliminary MRI results suggest that vascular-related WMH involving frontal-subcortical circuits, also known to be critical to the pathophysiology of depression (Matsuo *et al*. 2005), could add to the HF-related functional deficits in medial temporal structures, and increase the likelihood of the emergence of MDD in HF patients. Relevant to the latter point is the fact that, in previous voxel-based SPECT investigations of subjects with late-onset MDD, rCBF deficits in the temporal lobe were found to be directly related to the severity of periventricular WMH as assessed with MRI (Ebmeier *et al*. 1998). Finally, it should be mentioned that variable degrees of carotid obstruction might have contributed to the CBF reductions in our HF patients (Mathiesen *et al*. 2004). By magnifying the reduction of blood output to the brain, carotid obstructions could also add to the vulnerability of HF patients to develop functional deficits in the medial temporal region, and further increase the likelihood of the emergence of major depressive symptoms (Doraiswamy *et al*. 1999; Gruhn *et al*. 2001; Campbell *et al*. 2004).

Some of the between-group rCBF differences in our study were located closely to cerebrospinal fluid (CSF) spaces, mainly the lateral ventricles. Given the limited intrinsic spatial resolution of the ^{99m}Tc-HMPAO SPECT images, added to the smoothing procedure during SPM processing, we cannot exclude the possibility that partial volume effects due to ventricle dilatation might have influenced the detection of rCBF differences in adjacent gray-matter regions, such as the posterior hippocampus/parahippocampal gyrus. However, the use of a customized template based on our own SPECT images, which matched more closely the elderly population under study, led to a lesser degree of image deformation during the process of spatial normalization than would have occurred had we used the standard SPM template (which is based on young healthy subjects not displaying ventricle dilatation). Such a strategy is likely to have improved the spatial specificity of our analysis, minimizing the chance of significant findings to be confounded by poor image normalization (Gispert *et al*. 2003). Moreover, we found that a substantial proportion of the voxels showing significant between-group rCBF differences in the right posterior hippocampal and parahippocampal gray matter had coordinates located at distances that were clearly greater than the 12-mm extended border of the adjacent lateral ventricles. This indicates that the focus of between-group difference seen in that region can be at least partially attributed to a genuine rCBF reduction in the right posterior medial temporal cortex in the MDD-HF group.

Significant cognitive deficits were also present in our MDD-HF subjects, and were more severe than those presented by the non-depressed HF group. On the other hand, the results reported herein showed no significant correlations between the severity of cognitive dysfunction and rCBF values in the medial temporal lobe in HF subjects, thus suggesting that the relationship between rCBF in the latter brain region and depressive symptoms was not determined by the concomitant presence of cognitive deficits.

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It has been proposed that MDD associated with signs of cerebrovascular disease may respond more poorly to pharmacological treatment (Baldwin *et al.* 2004), although studies investigating specifically samples of subjects with MDD and HF have reported favorable response rates to antidepressant treatment (Alvarez & Pickworth, 2003; Roose, 2003). In our sample of MDD-HF patients, there was a considerable degree of improvement after treatment with SSRI antidepressants. This finding may suggest that despite the greater degree of functional brain impairment in HF patients with co-morbid MDD, such deficits do not seem to predict poor response to pharmacological antidepressant treatment. Moreover, there were no correlations between pre-treatment rCBF deficits and changes in HDRS scores after 8 weeks of treatment, which might further indicate that there is no relationship between the severity of functional brain deficits and antidepressant response patterns. However, such interpretation has to be made with great caution, given the modest size of the HF sample studied, as well as the fact that the majority of MDD-HF patients responded to medication, thus limiting the power of the correlational analyses performed.

There are other methodological limitations of our study that should be highlighted. The use of the HDRS may have biased our assessment of depression severity towards physical symptoms, a problem that would not have occurred had we chosen a scale focused on psychological features of depression, such as the Montgomery–Asberg Depressive Rating Scale (MADRS; Montgomery & Asberg, 1979). We attempted to minimize such bias by using the 31-item HDRS scale (Williams, 1988), which evaluates the severity of hopelessness, helplessness, self-esteem, psychological retardation and atypical features, in addition to the elements assessed by the traditional 17-item HDRS. By making that choice, we aimed to obtain a more balanced assessment of both the psychological and physical features of depression. Also, our cross-sectional study design prevented us from excluding the possibility that rCBF abnormalities represented state-dependent, non-specific correlates of depressive symptoms, rather than reflecting functional abnormalities caused as a direct consequence of HF. Further imaging investigations of HF patients with depressive symptoms, studied before and after effective antidepressant treatments, are needed to clarify this issue. If confirmed in subsequent studies, our findings of localized temporo-limbic functional abnormalities may help to clarify the pathophysiology of MDD associated with HF. Such findings may also warrant further investigation on the possible clinical usefulness of brain-imaging methods to identify HF subjects that could be particularly vulnerable to the development of major depressive symptoms.

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DECLARATION OF INTEREST

None.

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