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An investigation of changes in regional gray matter volume in cardiovascular disease patients, pre and post cardiovascular rehabilitation ☆

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ABSTRACT

Cognitive function decline secondary to cardiovascular disease has been reported. However, little is known about the impact of coronary artery disease (CAD) on the aging brain macrostructure or whether exercise training, in the context of cardiovascular rehabilitation, can affect brain structure following a coronary event. This study employed voxel-based morphometry of high resolution structural MRI images to investigate; 1) changes in regional gray matter volume (GMV) in CAD patients compared to age-matched controls, and 2) the effects of a six-month exercise-based cardiovascular rehabilitation program on CAD-related GMV decline. Compared to controls, significant decreases in regional GMV were found in the superior, medial and inferior frontal gyrus; superior and inferior parietal gyrus; middle and superior temporal gyrus and in the posterior cerebellum of CAD patients. Cardiovascular rehabilitation was associated with the recovery of regional GMV in the superior frontal gyrus, superior temporal gyrus and posterior cerebellum of the CAD patients as well as the increase in GMV in the supplementary motor area. Total and regional GMV correlated with fitness level, defined by the maximal oxygen consumption (VO_2max), at baseline but not after cardiovascular rehabilitation. This study demonstrates that cardiovascular disease can adversely affect age-related decline in GMV; and that these disease-related effects could be mitigated by moderate levels of exercise training as part of cardiovascular rehabilitation.

1. Introduction

According to the Institute of Medicine, the age standardized mortality rate from cardiovascular disease has declined steadily over the past 50 years in industrialized nations (IOM (Institute of Medicine), 2010). Much of the decline can be attributed to effective management of risk factors associated with the disease. However, in the developed world, cardiovascular disease still remains the most prevalent chronic disease in individuals over the age of 50, and the debilitating effects of the disease are evident by the high rate of hospitalization among this patient group (World Health Organization (WHO), 2011). Therefore, there is heightened urgency to understanding the impact of cardiovascular disease on 'successful aging', particularly given that the number of adults over the age of 60 is steadily increasing.

One growing concern is the potential link between cardiovascular disease risk factors and neurological impairment in older adults. Hypertension, diabetes and hyperlipidemia have been independently linked to abnormal changes in morphology and function of the aging brain (De Toledo Ferraz Alves et al., 2010). Older individuals with higher estimated risk of coronary artery disease (CAD) tend to have decreased brain volume, cerebral blood flow, and glucose metabolism in regions of the brain associated with cognitive function and, as such, are at a greater risk of dementia (De Toledo Ferraz Alves et al., 2010). Even in older adults with no clinical diagnosis of cardiovascular disease, decline in cardiac function is associated with deficits in cognitive function (Jefferson et al., 2007a), brain atrophy (Jefferson, 2010) and white matter hyperintensity (Jefferson et al., 2007b).

Despite the above studies involving cardiovascular risk factors, there have been no similar studies on the impact of cardiovascular disease,

Abbreviations: CAD, Coronary artery disease; CR, Cardiovascular rehabilitation; GMV, gray matter volume; METs, metabolic equivalents; MoCA, Montreal Cognitive Assessment; VBM, voxel-based morphometry; VO_2max, maximal oxygen consumption.

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more specifically CAD, on normal age-related changes in regional brain morphology. Coronary artery disease is the most common form of cardiovascular disease in adults over 50 years old with known pathophysiology (Chilton, 2004) and effective management strategies (Pflieger et al., 2011). Physical activity is one of the most powerful and readily available interventions with proven efficacy in preventing secondary CAD. Physical activity, specifically aerobic fitness has been shown to improve coronary flow, lower the risk of myocardial reinfarction, lower mortality rates, and improve overall cardiac function (Shephard and Balady, 1999). Consequently, increased levels of physical activity are increasingly prescribed as part of the clinical management for CAD (Smith et al., 2011). In older adults, physical activity has also been associated with improved cognitive function (Colcombe et al., 2004), decreased risk for dementia (Larson et al., 2006) and reversal of cortical decline (Colcombe et al., 2006).

These observations highlight the need to investigate the association between CAD and brain structure and whether interventions, such as physical activity, can reverse any adverse disease-related effects. The objectives of this study were twofold: 1) to investigate potential differences in regional gray matter volume in patients recently diagnosed with CAD compared to controls, and 2) to determine if a standard cardiac rehabilitation regimen would reverse CAD-related structural changes.

2. Methods

2.1. Participants

This study was approved by the Western University Health Sciences Research Ethics Board, and written informed consent was obtained from all subjects. CAD patients were recruited from the London Health Sciences Centre for Cardiac Rehabilitation and Secondary Prevention program following recent diagnosis of one of the following: acute coronary syndrome (ST elevation or non-ST elevation myocardial infarct), angina, percutaneous coronary intervention, or coronary artery bypass surgery. Patients were excluded if they had congenital coronary abnormality, cardiomyopathy, severe congestive heart failure, second or third-degree atrioventricular block, more than two myocardial infarcts, sick sinus syndrome, or major arrhythmias. Patients with uncontrolled hypertension or a history of diabetes for more than 5 years were also excluded. Age-matched control subjects included in this study had no clinical diagnosis of cardiovascular disease, were non-smokers, and did not have hypertension or diabetes. Both patients and controls were free of any neurological condition or disease.

2.2. Clinical assessments of health

The relevant clinical markers of CAD measured in all subjects are described below. A standard three-lead electrocardiogram was conducted after 20 min of supine rest. Blood pressure was continuously measured during electrocardiogram using a Finometer, which was calibrated against periodic sphygmomanometric measurements (Dinamp, GE Healthcare, Finland). Blood-borne markers of vascular disease namely: plasma lipids, cholesterol, high-sensitivity C-reactive protein (hsCRP) and glucose, were collected under fasting conditions. A Doppler echocardiography (GE/Vingmed System FiVe Doppler) was completed prior to cardio-respiratory exercise stress testing to assess left ventricular ejection fraction, left ventricular mass and left ventricular contractility. A test of global or overall cognitive function was performed with the Montreal Cognitive Assessment, MoCA (http://www.mocatest.org/). Cardiorespiratory fitness was measured by a graded exercise test in which subjects were tested to volitional exhaustion under standard clinical observation (ACSM, 1995). Breath-by-breath measurements of oxygen consumption (VO_2), heart rate and blood pressure were recorded throughout the test. Maximal oxygen consumption (VO_2max) is an established marker of cardiorespiratory fitness and a clinically accepted surrogate maker for left ventricular function (Fletcher et al., 2001). Each subject's VO_2max was estimated from the graded exercise test.

2.3. Clinical assessment of cardiac rehabilitation

The aerobic exercise component of the cardiac rehabilitation (CR) program was performed according to current guidelines (Stone et al., 2009) at an intensity of 40–70% of heart rate reserve (i.e., the difference maximum between the age-predicted and resting heart rates) (Karvonen et al., 1957), or at a rate corresponding to an exertion score of 11–14 on the Borg scale (Borg, 1982). Aerobic exercise was performed a minimum of 3 days per week at a duration of 20-to-30 min per session.

2.4. MRI data acquisition

Whole-brain MRI images were acquired on two Siemens 3 T MAGNETOM® Verio systems (Siemens Medical Systems, Erlangen, Germany) equipped with 32-channel head array coils. Sagittal T1-weighted images were acquired on each subject for gray matter volumetric analysis using a three-dimensional (3D) magnetization-prepared rapid gradient-echo imaging sequence (isotropic voxel resolution = 1.0 mm^3; repetition time, echo time and inversion time = 2000, 2.98 and 900 ms, respectively; acceleration factor = 3; and flip angle = 9°).

2.5. Voxel-based morphometry analysis

2.5.1. Effect of disease

T1-weighted images were segmented into gray matter (GM), white matter (WM) and cerebrospinal fluid (CSF) using the segmentation option in SPM8 (http://www.fil.ion.ucl.ac.uk). The tissue segments were then affine-registered to their respective Montreal Neurological Institute (MNI) tissue probability maps, averaged and smoothed with a 12-mm filter using DARTEL to create a study-specific template (Ashburner, 2007). The individual GM images were spatially normalized to this template using a high-dimensional DARTEL registration and then multiplied by the Jacobian determinant (i.e., modulation) to correct for nonlinear differences in individual brain size. Finally, the GM images were smoothed with an 8-mm Gaussian filter. Local differences in GM volume (GMV) between groups were investigated with a gender-by-group two-factor analysis of variance, performed on the smoothed GMV images. An absolute threshold mask set at 0.1 was used to remove non-GM and extra-cranial effects. A significant positive effect of disease was identified at voxel levels that differed between groups at $p < 0.05$ after correction for multiple comparisons using the false discovery rate (FDR) (Genovese et al., 2002).

2.5.2. Effect of rehabilitation

Pre and post CR T1-weighted images of the CAD patients were analyzed with the default options of the longitudinal module found in the VBM8 toolbox of SPM8. Briefly, each subject's data were analyzed in a series of steps that included: 1) intra-subject registration, 2) intra-subject bias correction, 3) segmentation, 4) non-linear DARTEL registration to study-specific template, 5) modulation of GM segments, and 6) spatial smoothing with an 8 mm Gaussian filter. A repeated measures analysis of variance of the change in GM volume over time was performed on the smoothed GM image with a within-subject factor of time and between-subject factor of scanner. Gender-by-time analysis of variance was also explored. A positive significant change was identified at voxel levels that showed positive change in volume for $p < 0.05$ after correction for multiple comparisons using the more stringent family wise error (FWE) (Genovese et al., 2002). An absolute threshold mask was also set at 0.1.

To investigate evidence of GMV recovery with CR, binary masks of regions of interests (ROIs) were created using the MarsBaR ROI toolbox (http://marsbar.sourceforge.net) from clusters of voxels that showed

statistically in significant decline GMV in the CAD group compared to controls (see Table 2) with minimum voxel clusters of 50 contiguous voxels. Small volume correction was performed in SPM8 on contrast images from the repeated analysis of variance with the ROIs to restrict multiple comparisons to a smaller number of voxels, which reduced type II errors. Areas of GM recovery are reported as significant if clusters survive FWE correction at $p < 0.05$.

2.5.3. Statistical analysis

Statistical analyses were conducted with SPSS 20.0 statistical software (IBM Corp. Armonk, NY, and USA). Clinical assessments from the control group was compared to baseline data from the CAD patient group using a one-way multivariate analysis of variance to test for differences in cardiovascular health and cognitive function. Clinical parameters entered into the multivariate analysis for cardiovascular health include all variables listed in Table 1 except for age, gender, MoCA and VO_2max. Gender differences between groups was assessed by gender-by-group interaction and simple main effects of gender. Significant interaction and main effects are reported at $p < 0.05$. Spearman rank correlation analysis was performed between baseline total gray matter/ROI volumes and baseline MoCA scores, VO_2max and other clinical measures collected to investigate the association between overall cognition, fitness level, cardiovascular health, and brain atrophy. Total gray matter volume in mm^3 for each subject was obtained from the VBM8 segmentation output, while mean values of regional gray matter volume were extracted from voxel clusters that showed significant difference between groups for each subject using MarsBaR, as described earlier.

A paired *t*-test was conducted on the clinical variables collected on the CAD patients pre and post CR to test for a difference between the means ($p < 0.05$). To test for association between fitness level and GMV post CR, a Spearman rank correlation analysis was performed between VO_2max and total gray matter/ROI volumes obtained from post CR data, and between change in GMV and change in VO_2max post CR.

3. Results

3.1. Cardiovascular disease effects

A total of 41 CAD patients and 21 controls participated in the study; their characteristics are provided in Table 1. Data from three controls and two CAD patients data were removed because of neurological incidental findings in the MRI data. Data from 36 patients and all controls were collected on one scanner, while data from the last 5 patients were acquired on a separate, but identical, scanner during the upgrade of the first one. All control subjects and 18 CAD patients completed the graded exercise testing with cardiorespiratory measures to maximum volitional exhaustion to establish maximal oxygen uptake (VO_2max).

Table 1
Study participant characteristics. The mean and standard deviation are presented for clinical variables measured at baseline in CAD patients and controls.

Variable	Controls (n = 21)	Pre-CR CAD patients (n = 39)
Age	59 ± 8	59 ± 7
Gender (men/women)	11/10	28/11
BMI	24.8 ± 3.3	29.8 ± 4.7[a]
Fasting blood glucose (mmol/L)	4.75 ± 0.88	5.23 ± 1.32
Total cholesterol (mmol/L)	4.17 ± 0.94	3.16 ± 0.79[a]
hsCRP (mg/L)	0.95 ± 0.89	2.25 ± 3.10[a]
Rest supine systolic blood pressure (mm Hg)	121 ± 16	127 ± 22
Rest supine diastolic blood pressure (mm Hg)	69 ± 8	71 ± 12
Left ventricular ejection fraction (%)	68 ± 9	64 ± 8
Resting heart rate (beats per minute)	59 ± 10	59 ± 7
MoCA	28.16 ± 1.7	26.86 ± 2.1[a]
VO_2max (mL/min/kg)	37 ± 2	26 ± 2[a]

[a] Statistical difference between groups at $p < 0.05$.

The CAD group comprised of patients with clinical diagnosis at referral of angina (12.1%), myocardial infract (12.1%) and coronary artery disease (69.7%). All patients were on a combination of drug therapy and 36.8% had percutaneous coronary intervention while 7.9% received coronary artery bypass grafting. Drug therapy included cholesterol lowering/statins (87.2%), beta-blockers (76.9%), ACE-inhibitors/angiotensin II receptor blockers (56.4%) and anti-platelets including aspirin (84.6%). There were no significant interactions between gender and group for any of the clinical measures, including markers of fitness. No significant differences between patients and controls were found for measures of blood pressure, cardiac output, left ventricular ejection fraction, resting heart rate and blood glucose. However, compared to control, CAD patients had lower MOCA scores ($F = 4.3$ (1,53), $p < 0.05$), lower VO_2max ($F = 17.04$ (1,53), $p < 0.001$), lower total cholesterol levels ($F = 16.22$ (1,56), $p < 0.001$), elevated body mass index, BMI ($F = 17.86$ (1,56), $p < 0.001$), and increased hsCRP levels ($F = 7.40$ (1,55), $p < 0.01$). There was also significant difference in level of education ($p = 0.031$), as defined by the number of years of formal education, between patients (15.5 ± 2.7 years) and controls (18.3 ±4.3 years).

VBM results of regional GMV differences between patients and controls are shown in Fig. 1, and the corresponding MNI coordinates and Talairach anatomical labels are listed in Table 2. In general, the CAD patient group exhibited significantly lower GMV in the frontal lobe, parietal lobe, temporal lobe, and cerebellum. There was a significant difference in total GMV ($F = 5.5$ (1, 53), $p < 0.05$) between groups but no statistical difference in total intracranial volume. There were moderate positive associations between VO_2max and total GMV ($\rho = 0.420$(38), $p < 0.001$), and GMV in the left posterior cerebellum ($\rho = 0.616$ (38), $p < 0.001$) and right post central gyrus ($\rho = 0.403$ (38), $p < 0.01$). There was no significant gender-by-group interaction, nor was there any correlation between total/regional GMV and MoCA scores or any other clinical parameter measured. Repeating the VBM analysis after removing the data from the 5 patients acquired on the second system had no effect on these results, except to reduce the effect size of the observed regional changes by 5 ± 13%.

3.2. Effects of cardiac rehabilitation

Twenty-four CAD patients (18 men and 6 women) completed the 6-monthCR program and post-CR testing. The MRI data, pre and post-rehabilitation, from the last five patients were acquired on the second scanner. Fifteen patients completed graded exercise testing to maximum volitional exhaustion on entry and exit from the CR program. No statistically significant differences were found in any of the clinical parameters between the pre and post-CR tests. In addition, there was no change in MoCA scores ($p = 0.3$) after 6 months of CR. There was a trend (5%) towards increased VO_2max ($p = 0.06$) in the 15 patients tested after 6 months of CR.

Regions of positive change in GMV from VBM analysis of CAD patients, pre and post-CR, are listed in Table 3 and displayed on Fig. 2. The main increases in GMV after 6 months of CR were observed bilaterally in the frontal lobe, middle temporal gyrus and supplementary motor area (Table 3). Small clusters of increase in GMV were observed in some of the regions affected by CAD (see Table 4), signifying a recovery of volume following CR. There was no change in total GMV or total intracranial volume after CR. No significant correlation was found between VO_2max post CR and regional GMV and between change in VO_2max and regional increase in GMV. There was no significant scanner-by-time interaction or gender-by-time interaction ($p < 0.05$, FWE) and no difference in GMV or clinical measures between patients

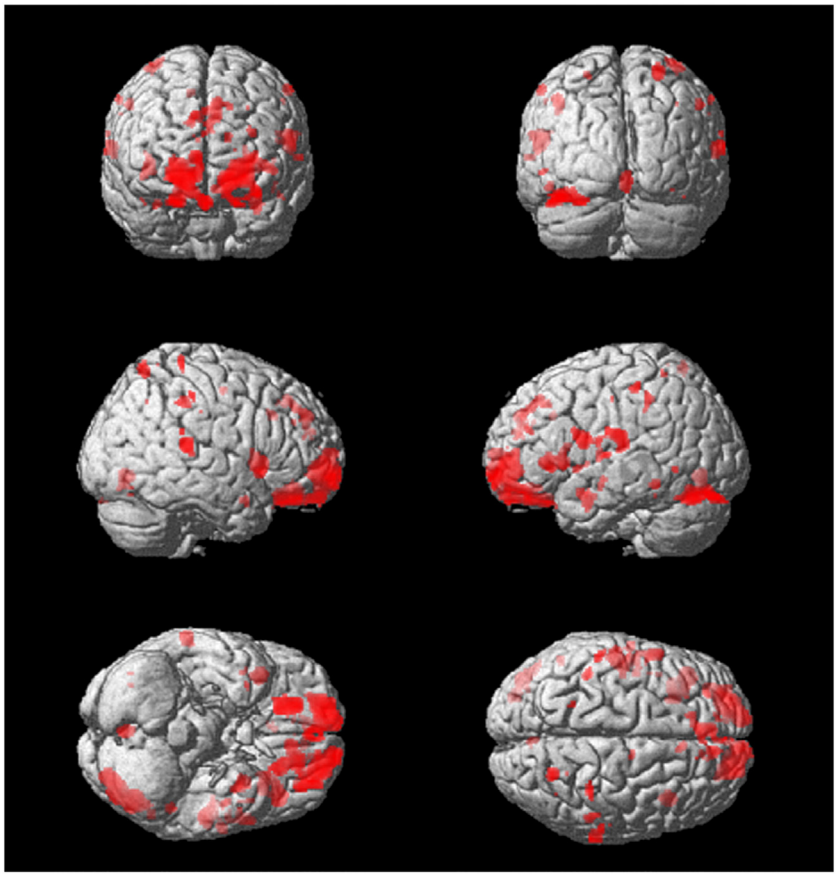

Fig. 1. Differences in GMV between CAD patients and age-matched controls measured at baseline. t-Statistics displayed on a rendered model of a single subject brain. The red blobs on coronal, sagittal and transverse planes indicate areas of decreased GMV in the CAD patient group.

Table 2
Local maxima of clusters of significant change in GM volume in the pre-CR CAD patient group compared to controls. Coordinates are given in anatomical MNI space and maxima are shown at least 8.0 mm apart. The center of mass of each ROI is shown in bold. (Corrected for multiple comparisons (FDR, $p < 0.05$).

Cluster Number	Volume (mm)	Anatomical label	Brodmann area	MNI coordinate			t-Value
				x	y	z	
1	2688	**L superior frontal gyrus**	**10**	**−22**	**57**	**−10**	**5.03**
		L SFG	10	−18	55	−23	3.00
		L MFG	11	−27	45	−6	4.66
2	1831	**R superior frontal gyrus**	**10**	**18**	**58**	**−10**	**4.96**
		L frontal lobe (rectal gyrus)	11	0	48	−23	4.76
		R SFG	10	14	54	−15	3.81
3	1515	**L posterior cerebellum**	**NA**	**−40**	**−68**	**−12**	**4.90**
4	510	R posterior cerebellum	NA	3	−73	−3	4.73
5	799	**R medial frontal gyrus**	**9**	**9**	**47**	**29**	**4.64**
		L medial frontal gyrus	8	−6	45	29	3.74
6	674	R inferior frontal gyrus	47	42	15	−3	4.52
7	977	**L parietal lobe (post central gyrus)**	**40**	**−56**	**−20**	**19**	**4.42**
		L Frontal (precentral gyrus)	4	−51	−13	42	3.74
8	202	**L inferior frontal gyrus**	**44**	**−53**	**4**	**16**	**4.41**
		L parietal (precentral)	4	52	−5	15	3.50
9	774	**R orbitofrontal**	**11**	**22**	**38**	**−22**	**4.33**
10	1601	**L IFG**	**47**	**−42**	**28**	**−1**	**4.31**
		L Insula		−33	17	0	4.01
11	134	L inferior parietal gyrus	40	−42	−36	41	4.13
12	518	R inferior parietal lobe	40	51	−33	40	4.07
13	83	L middle temporal gyrus	37	−51	−55	0	4.02
14	127	R superior parietal gyrus	7	24	−58	61	3.96
15	141	L temporal lobe (Fusiform)	37	−50	−42	−10	3.71
16	270	L superior temporal gyrus	38	−33	5	−17	3.63
17	50	R superior temporal gyrus	38	44	3	−19	3.50
18	69	R inferior temporal gyrus	20	39	−22	−31	3.45
19	74	R anterior cingulate gyrus (dorsolateral)	32	6	25	30	3.38

L = left; R = right; SFG = superior frontal gyrus; MFG = medial frontal gyrus; IFG = inferior frontal gyrus.

Table 3
Local maxima of clusters of significant change in GM volume in the CAD post CR (Post > Pre). Coordinates are given in anatomical MNI space, and maxima shown are at least 8.0 mm apart. The center of mass of each ROI is shown in bold. Corrected for multiple comparisons (FWE, $p < 0.05$).

Cluster Number	Volume (mm)	Anatomical label	Brodmann Area	MNI Coordinate			t-Value
				x	y	z	
1	1095	Right frontal (paracentral) lobe	6	8	−33	66	13.67
2	304	Left middle temporal gyrus	21	−62	−60	9	11.63
3	504	Left frontal (paracentral) lobe	6	−8	−28	66	10.70
4	782	**Right anterior cerebellum**	NA	**3**	**−55**	**4**	**10.37**
		Left posterior cerebellum	NA	0	−73	−8	8.92
		Left cerebellum	NA	−8	−81	−15	8.44
5	191	Right superior frontal gyrus	10	22	63	−8	10.26
6	122	Left inferior temporal gyrus	20	−32	0	−47	8.88
7	1175	Right superior temporal	38	22	8	−45	8.88
8	427	**Right superior temporal**	**22**	**64**	**−42**	**10**	**8.12**
		Right middle temporal gyrus	22	66	−34	4	7.84
9	246	Right frontal (precentral) gyrus	6	56	0	31	7.79
10	28	Left superior temporal gyrus	22	−56	11	−2	7.33
11	54	Left medial frontal gyrus	10	−3	66	6	7.27
13	93	Right medial frontal gyrus	6	4	−19	54	7.13

that successfully completed exercise testing and patients that were unable to.

4. Discussion

The key findings of the current study were lower GMV in the prefrontal cortex, parietal and temporal lobes of CAD patients compared to age-matched controls (Fig. 1 and Table 2) and increased GMV in the superior frontal gyrus, medial frontal gryus and superior temporal gryus after 6 months of cardiovascular rehabilitation (Fig. 2 and Table 3). This study is the first to show evidence of regional cortical brain atrophy associated with cardiovascular disease and also the ability of cardiovascular rehabilitation to reverse disease-related cortical atrophy.

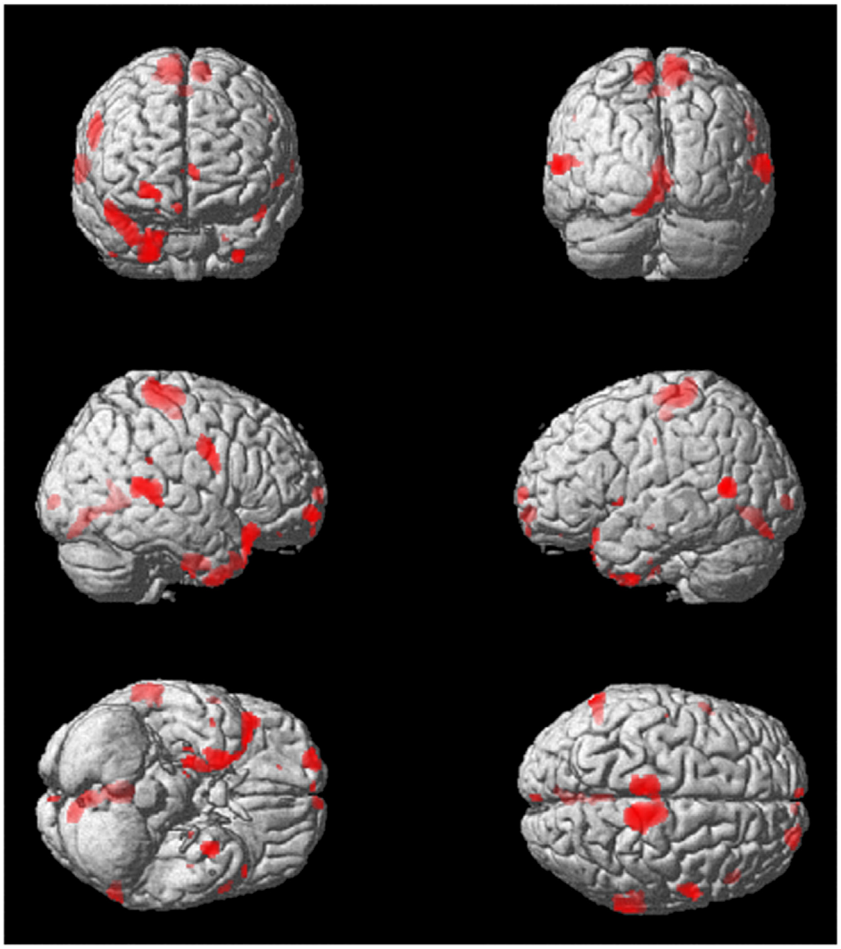

Fig. 2. GMV changes over time in CAD patient pre and post CR. t-Static displayed on a rendered model of a single subject brain. Red blobs on coronal, sagittal and transverse planes indicate areas of increased GMV in the CAD group after 6 months of CR.

Table 4
Cluster of GMV recovery after 6 months of CR (N = 24). Small volume correction (p < 0.05, FWE).

Cluster Number	Volume (mm)	Anatomical label	Brodmann Area	MNI Coordinate			t-Value
				x	y	z	
1	128	Right superior frontal gyrus	11	22	61	−10	10.26
2	23	Right middle temporal gyrus	22	67	−37	13	7.20
3	99	Left posterior cerebellum (declive of vermis)	NA	0	−72	−3	8.92

4.1. Cardiovascular disease effects

Our CAD group was composed of patients diagnosed with either angina or myocardial infarction who were all receiving some form of treatment prior to the start of the study. Most patients were on a combination of drug therapy to lower lipid levels, to maintain blood pressure, and to prevent reinfarction. The therapeutic impact of these treatments might have contributed to the lack of any statistical differences in fasting blood glucose, resting supine blood pressure, cardiac output or heart rate between patients and controls. The CAD patients had lower lipid levels compared to controls, which can be attributed to the efficacy of statins in reducing serum levels of cholesterol (Cholesterol Treatment Trialists' (CTT) Collaborators et al., 2012). However, mean hsCRP, a marker of inflammation associated with increased risk of myocardial infarct or reinfarction, was higher for CAD patients than controls.

4.2. CAD-related effects: Brain atrophy

The findings of decreased GMV in the frontal, temporal and parietal lobes of CAD patients are similar to the patterns of brain atrophy previously observed in patients with either hypertension or diabetes, in which marked declines in GMV were found in the prefrontal cortex, superior temporal and middle temporal lobes, thalamus, and hippocampus (De Toledo Ferraz Alves et al., 2010). The regions common to all of these studies are associated with varying cognitive functions – executive function, attention, and memory, visuospatial and psychomotor speed – and are believed to be susceptible to vascular disease (Nordlund et al., 2007). A study of 400 men over the age of 40 found that cardiovascular disease was associated with poor performance in memory tests and a trend towards lower scores in mini-mental state examination (MMSE) (Muller et al., 2007). Similarly, Okonkwo et al. (2010) reported an accelerated decline in the aforementioned cognitive domains in a large group of cardiovascular disease patients over a three year period that was not attributed to aging. In addition, numerous studies have linked markers of cardiovascular disease including impaired vascular hemodynamics (pulse wave variability, arterial stiffness, and ventricular function) to alterations in cognitive function (Fujiwara et al., 2005; Wendell et al., 2009). In general, the observation of decreased GMV in the frontal, temporal and parietal lobes indicates that CAD accelerates age-related neocortical degeneration, possibly leading to a declining cognitive function.

Our findings of bilateral atrophy in the posterior cerebellum and in the inferior parietal lobule of the brain in the CAD group is novel given that these regions are usually preserved with age and atrophy has only been reported in a few dementia studies (Greene et al., 2010; Yoon et al., 2013). These studies linked poor performance on short-term memory and visuospatial tasks to GMV decline in either the cerebellum (Yoon et al., 2013) or the inferior parietal lobule (Greene et al., 2010), highlighting the known importance of both regions in neurocognitive integration. Taken together, these observations suggest that in older adults, cardiovascular disease can precipitate changes in normally stable regions of the brain.

A significant difference in mean baseline MoCA scores between the CAD group and controls was found in the current study (Table 1). 24% of CAD patients had a score of 25 or less compared to 5% of controls. A MoCA score of less than 26 is typically considered to reflect mild cognitive impairment (MCI). However, there was no correlation between MoCA scores and regional brain atrophy. Considering the MoCA is a brief assessment tool of MCI (Nasreddine et al., 2005), it may not be ideal for probing subtle cognitive decline in middle-aged adults since evidence of cognitive decline typically occurs after the age of 60 (Hedden and Gabrieli, 2004). The apparent difference in MoCA scores between groups could possibly be a mere reflection of the difference in levels of education observed between groups. Education was associated with performance on MoCA ($r = 0.518$, $p < 0.01$), but not total or regional GMV. Similarly, Christensen et al. (2009) found no link between level of education and global or regional brain atrophy in adults with no history of cognitive impairments. The use of tests more specific to the cognitive functions associated with the observed areas of brain atrophy might reveal greater impairment. Nonetheless, the current data support the overall concern that CAD accelerates cortical atrophy with detrimental outcomes to cognitive ability.

The direct mechanism(s) that drive the greater brain atrophy associated with cardiovascular disease are unclear. One possible mechanism could involve cerebral hypoperfusion. Animal studies have shown that cerebral hypoperfusion from ischemic vessels can initiate pathophysiological changes in the brain structure and function of aging rats, resulting in decreased synaptic activity and impaired memory and visuospatial skills (De la Torre, 2000). Human studies of diabetic and hypertensive patients have reported regional cerebral hypoperfusion in similar regions of the brain where atrophy has been reported (Dai et al., 2008; Last et al., 2007). Investigating cerebral blood flow or cerebrovascular dynamics with morphometric imaging would help elucidate potential neurovascular changes in CAD patients.

A common cause underlying both CAD and brain atrophy could be physical inactivity. Physical inactivity is an important modifiable risk factor for heart disease given that inactive individuals are twice as likely to suffer a coronary event in their lifetime compared to physically active individuals (Powell et al., 1987). In this study, the CAD patients were 40% less fit than controls and the less fit individuals were more likely to have lower global and regional GMV. In general, physical inactivity is associated with regional brain atrophy (Yuki et al., 2012) and cognitive decline (Barnes et al., 2003) in healthy older adults.

4.3. Effect of rehabilitation: Neuroplasticity

The propensity for age and CAD to adversely affect the function and morphology of certain regions of the brain, namely the prefrontal, superior parietal, inferior temporal and middle temporal, suggests that these regions are highly malleable and perhaps more adaptive to change. Recovery of volume within these brain regions with exercise in both healthy aging subjects and dementia patients signifies that these regions are highly plastic (Colcombe et al., 2004; Erickson et al., 2012; McAuley et al., 2004). These observations are in good agreement with our finding of increased GMV in the prefrontal, left middle temporal, left inferior temporal lobes in addition to the cerebellum, supplementary motor areas and right superior temporal gyrus of CAD patients after 6 months of CR.

The significance of aerobic fitness in improving cardiovascular and cerebral functions is well established and discussed in great detail in reviews by Erickson et al. (2010) and Lavie et al. (2009). Briefly, with CAD, aerobic fitness is associated with a significant decrease in relative risk of mortality, improved ventricular function, and improved vascular dynamics (Baker et al., 2010). In older adults and dementia patients, exercise training was associated with increases in regional brain volume, improved cognitive function, and increased neuronal activity (Lavie et al., 2009). Increases in regional GMV (Colcombe et al., 2006; Lautenschlager et al., 2008) and cognitive function (Erickson et al., 2010) have been reported after 6 months of moderate level of exercise training (40–70% of heart rate reserve). The prescribed 6 months of aerobic exercise, as part of the CR program, was sufficient to cause detectable changes in brain

structures of CAD patients including changes in non-motor areas, despite the observed modest impact on aerobic fitness.

Findings of recovery of GMV in areas of the superior frontal lobe, superior temporal lobe and posterior cerebellum (Table 4) after a short period of exercise are promising and indicate a unique positive outcome of CR. It could be postulated that the recovery of brain volume in these regions could potentially be maintained over longer periods. Erickson et al. (2010) found retention of regional brain volume in older adults that performed low intensity exercise nine years after cessation of the activity.

4.4. Study consideration

The impact of cardiac artery bypass grafting surgery (CABG) on neuroanatomy and cognitive function cannot be ignored. CABG is known to exert transient decrease in brain volume and cognitive function (Selnes and McKhann, 2005). The interaction between cardiovascular disease and CABG on regional GMV was not explored given that only 8% of CAD patients in this study underwent CABG and this occurred a few months prior to the start of the study.

It is possible that the GMV changes observed post-CR in CAD patients might not reflect the full potential neurorehabilitatory benefits of CR giving the moderate improvement in GMV post exercise training. Considerable changes could be achieved with either high-intensity aerobic exercises or activities such as basket ball, hockey or squash that incorporate motor skills along with cognitive and perceptual skills (areas which showed significant GMV decline with CAD). The lack of association between VO_2max and GMV could be a result of the large number of patients who were unable to complete the graded exercise test for various reasons including the inability to reach maximal volitional exhaustion, which is common among CAD patients. Submaximal graded exercise tests or a 6 minute walk test could be used to evaluate cardiorespiratory capacity in CAD patients who cannot achieve maximal myocardial oxygen uptake. However, submaximal VO_2 tests often lack diagnostic accuracy, particularly tests that exclude heart rate measures with electrocardiography.

The innate methodological limitations of VBM are also drawbacks to the interpretation of our findings. The registration, segmentation and normalization steps in VBM can introduce bias and distortion errors particularly in the border of small subcortical GM structures where some proximal voxels can be misclassified (Ashburner and Friston, 2000; Good et al., 2001). This error is exaggerated in older brains prone to enlarged ventricles. We minimized these distortion errors with the use of a study-specific template and DARTEL registration method (Ashburner, 2007; Good et al., 2001). However, this inherent segmentation and registration bias can pose a limitation to the investigation of CAD-related regional brain volume changes in vulnerable subcortical regions such as the hippocampus where decline in volume have been previously reported in CAD (Koschack and Irle, 2005). For longitudinal studies, available intra-subject bias correction methods attempt to minimize the influence of baseline differences on images from subsequent time points. However, issues of registration asymmetry can be largely improved with symmetric diffeomorphic approaches proposed for future versions of SPM, particularly for non-quantitative T1-imaging data (Ashburner and Ridgway, 2013).

A potential limitation with this study was the use of two scanners in data acquisition. However, performing the analysis of the effects of CAD without the five patients imaged on the second scanner revealed no difference in the pattern of regional GMV differences reported in Table 2 and shown in Fig. 1. Furthermore no significant effect was found by including scanner as a between-subject factor in the analysis of the rehabilitation data.

5. Conclusion

This study demonstrates that in stable CAD patients, cardiovascular disease is associated with brain atrophy in several brain regions, including those related to cognitive ability. This disease-related effect appears to be reversible as this study demonstrated that a modest aerobic program reversed some of the structural abnormalities.

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