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

U.C. Anazodo a,b,c, J.K. Shoemaker c, N. Suskin a,d, K.S. St. Lawrence a,b

a Lawson Health Research Institute, London, ON, Canada
b Department of Medical Biophysics, Western University, London, ON, Canada
c Laboratory for Brain and Heart Health, School of Kinesiology, Western University, London, ON, Canada
d Cardiac Rehabilitation Program, Division of Cardiology, Western University, London, ON, Canada

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,

Abstract article info

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 max-

Keywords: Coronary artery disease Exercise training Neuroplasticity Regional brain atrophy Voxel-based morphometry

Abbreviations: CAD, Coronary artery disease; CR, Cardiovascular rehabilitation; GMV, gray matter volume; METs, metabolic equivalents; MoCA, Montreal Cognitive Assessment; VBM, voxel-based morphometry; VO2max, maximal oxygen consumption.

☆ This is an open-access article distributed under the terms of the Creative Commons Attribution-NonCommercial-No Derivative Works License, which permits non-commercial use, distribution, and reproduction in any medium, provided the original author and source are credited.

Corresponding author at: Lawson Health Research Institute, 268 Grosvenor Street, London, ON N6A4V2, Canada. Tel.: +1 519 646 6100 x65732; fax: +1 519 646 6205.

E-mail address: uanazodo@lawsonimaging.ca (U.C. Anazodo).

Available online 6 October 2013

Accepted 29 September 2013

Received 28 June 2013

Article history:

http://dx.doi.org/10.1016/j.nicl.2013.09.011

© 2013 The Authors. Published by Elsevier Inc. All rights reserved.
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 (Pfleger 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 infarction, 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 (VO₂), heart rate and blood pressure were recorded throughout the test. Maximal oxygen consumption (VO₂max) is an established marker of cardiorespiratory fitness and a clinically accepted surrogate maker for left ventricular function (Fletcher et al., 2001). Each subject’s VO₂max 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 mm³; 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.filion.uc.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 VO2max. 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, VO2max 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<sup>3</sup> 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 VO2max and total gray matter/ROI volumes obtained from post CR data, and between change in GMV and change in VO2max 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 neurologically 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 (VO2max).

The CAD group comprised of patients with clinical diagnosis at referral of angina (12.1%), myocardial infarct (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 VO2max (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 VO2max and total GMV (F = 0.420 (38), p = 0.001), and GMV in the left posterior cerebellum (p = 0.616 (38), p = 0.001) and right post central gyrus (p = 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-month CR 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 VO2max (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 VO2max post CR and regional GMV and between change in VO2max 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.

| Variable              | Controls (n = 21) | Pre-CR CAD patients (n = 39) |
|-----------------------|------------------|-----------------------------|
| Age                   | 59 ± 8 (7)       | 59 ± 7 (7)                  |
| Gender (men/women)    | 11/10            | 28/11                       |
| BMI                   | 24.8 ± 3.3       | 29.8 ± 4.7*                 |
| 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*                |
| hsCRP (mg/L)          | 0.95 ± 0.89      | 2.25 ± 3.10*                |
| 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*                |
| VO2max (mL/min/kg)    | 37 ± 2           | 26 ± 2*                     |

* Statistical difference between groups at p < 0.05.
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 (x, y, z) | t-Value |
|---------------|-------------|------------------|---------------|--------------------------|---------|
| 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            | 1901        | 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.
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 pre-frontal 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 gyrus and superior temporal gyrus 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.

### 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 |
|----------------|-------------|-----------------------------------------|---------------|----------------|---------|
| 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    |

**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.

392  U.C. Anazodo et al. / NeuroImage: Clinical 3 (2013) 388–395
We are a team of experts who can help you with any writing or research-related task. Please let us know how we can assist you.
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 neuropsychology 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 VO2max 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 VO2 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 Irisle, 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.

Role of the funding source

This work was supported by funding from the Heart and Stroke Foundation of Ontario (Grant number: T 6334). N. Suskin was supported in part by Western University Department of Medicine Program of Experimental Medicine (POEM) Research Award POEM. The funding sources had no role in the study design, collection, analysis, interpretation of data, writing of this manuscript or in the decision to submit the article for publication.

References

ACSM, 1995. Guidelines for Exercise Testing and Prescription, 5th ed. Lippincott Williams and Wilkins, Philadelphia, Pa 160.

Ashburner, J., 2007. A fast diffeomorphic image registration algorithm. NeuroImage 38, 95–113.

Ashburner, J., Friston, K.J., 2000. Voxel-based morphometry—the methods. NeuroImage 11, 805–821.

Ashburner, J., Ridgway, G.R., 2013. Symmetric diffeomorphic modeling of longitudinal structural MRI. Front. Neurosci. (5), 197 (Feb.).

Baker, L.D., Frank, L.L., Foster-Schubert, K., Green, P.S., et al., 2010. Effects of aerobic exercise on mild cognitive impairment: a controlled trial. Arch. Neurol. 67, 71–79.

Barnes, D.E., Yaffe, K., Sataniarn, W.A., Tager, I.B., 2003. A longitudinal study of cardiorespiratory fitness and cognitive function in healthy older adults. J. Am. Geriatr. Soc. 51, 450–464.

Borg, G.A., 1982. Psychophysical bases of perceived exertion. Med. Sci. Sports Exerc. 14, 377–381.

Chilton, R.J., 2004. Pathophysiology of coronary heart disease: a brief review. J. Am. Diet Assoc. 104, 55–58.

Cholesterol Treatment Trials’ (CTT) Collaborators, Mikhailova, B., Emmerson, J., Blackwell, L., et al., 2012. The effects of lowering LDL cholesterol with statin therapy in people with low risk of vascular disease: meta-analysis of individual data from 27 randomised trials. Lancet 380 (9814), 581–590.

Christensen, H., Batterham, P.J., Mackinnon, A.J., Anstey, K.J., Wen, W., Sachdev, P.S., 2009. Education, aptitude and cognitive change in an epidemiological sample in early old age. Am. J. Geriatr. Psychiatry 17 (3), 218–226.

Colcombe, S.J., Kramer, A.F., Erickson, K.I., Scalf, P., McAuley, E., Cohen, N.J., Webb, A., Jerome, G.J., Marquez, D.X., Elavsky, S., 2004. Cardiovascular fitness, cortical plasticity, and aging. Proc. Natl. Acad. Sci. U. S. A. 101, 3316–3321.

Colcombe, S.J., Erickson, K.I., Scalf, P.E., Kins, J.S., Prakash, R., McAuley, E., Elavsky, S., Marquez, D.X., Hu, L. Kramer, A.F., 2006. Aerobic exercise training increases brain volume in aging humans. J. Geronotol. 61, 1166–1170.

Dal, W., Lopez, O.L., Carmichael, O.T., Becker, J.T., Kuller, L.H., Gach, H.M., 2008. Abnormal regional cerebral blood flow in cognitively normal elderly subjects with hypertension. Stroke 39, 349–354.

De la Torre, J., 2000. Critically attained threshold of cerebral hypoperfusion: the CATCH hypothesis of Alzheimer’s pathogenesis. Neurobiol. Aging 21, 331–342.

De Toledo Ferraz Alvarez, T.C., Ferreira, L.C., Wajngarten, M., Busatto, G.F., 2010. Cardiovascular disorders as risk factors for Alzheimer’s disease. J. Alzheimers Dis. 20, 749–763.

Erickson, K.I., Raji, C.A., Lopez, O.L., Becker, J.T., Rosano, C., Newman, A.B., Gach, H.M., Thompson, P.M., Ho, A.J., Kuller, L.H., 2010. Physical activity predicts gray matter volume in late adulthood: the Cardiovascular Health Study. Neurology 75, 1415–1422.

Erickson, K.I., Miller, D.L., Weinlein, A.M., Aldi, S.L., Banducci, S., 2012. Physical activity, cortical plasticity in late adulthood: a conceptual and comprehensive review. Ageing Res. 4, 65.

Fletcher, G.F., Balady, G.J., Amsterdam, E.A., Chaitman, B., Eckel, R., Fleg, J., et al., 2001. Exercise standards for testing and training: a statement for healthcare professionals from the American Heart Association. Circulation 104, 1694–1740.

Fujiwara, Y., Chaves, P.H., Takahashi, R., et al., 2005. Arterial pulse wave velocity as a marker of poor cognitive function in elderly community-dwelling population. J. Geronotol. A Biol. Sci. Med. Sci. 60, 607–612.

Fujimura, C.R., Lazar, N.A., Nichols, T., 2002. Thresholding of statistical maps in functional neuroimaging using the false discovery rate. NeuroImage 15, 870–878.

Good, C.D., Johnsni, L.S., Ashburner, J., Henson, R.N., Friston, K.J., Fackowiak, R.S., 2001. A voxel-based morphometric study of aging in 465 normal adult human brains. NeuroImage 14, 21–36.

Greene, S.J., Killany, R.J., ADNI, 2010. Subregions of the inferior parietal lobule are affected in the progression to AD. NeuroImage 51, 354.

Greene, S.J., Killany, R.J., ADNI, 2010. Subregions of the inferior parietal lobule are affected in the progression to AD. NeuroImage 51, 354.

Hedden, T., Gabrieli, J.D., 2004. Insights into the aging mind: a view from cognitive neuroscience. Nat. Rev. Neurosci. 5, 87–96.

IOM (Institute of Medicine), 2010. Promoting Cardiovascular Health in Developing World: A Critical Challenge to Achieve Global Health. The National Academic Press, Washington, DC.
