Impact of weight loss on brain age: Improved brain health following bariatric surgery

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A R T I C L E  I N F O

Keywords:
Brain age
Weight loss
Bariatric surgery
Voxel-based morphometry

A B S T R A C T

Individuals living with obesity tend to have increased brain age, reflecting poorer brain health likely due to grey and white matter atrophy related to obesity. However, it is unclear if older brain age associated with obesity can be reversed following weight loss and cardiometabolic health improvement. The aim of this study was to assess the impact of weight loss and cardiometabolic improvement following bariatric surgery on brain health, as measured by change in brain age estimated based on voxel-based morphometry (VBM) measurements. We used three distinct datasets to perform this study: 1) CamCAN dataset to train the brain age prediction model, 2) Human Connectome Project (HCP) dataset to investigate whether individuals with obesity have greater brain age than individuals with normal weight, and 3) pre-surgery, as well as 4, 12, and 24 month post-surgery data from participants \((n = 87, \text{age: } 44.0 \pm 9.2 \text{ years}, \text{BMI: } 43.9 \pm 4.2 \text{ kg/m}^2)\) who underwent a bariatric surgery to investigate whether weight loss and cardiometabolic improvement as a result of bariatric surgery lowers the brain age. As expected, our results from the HCP dataset showed a higher brain age for individuals with obesity compared to individuals with normal weight (\(T\)-value \(= 7.08, \text{p-value} < 0.0001\)). We also found significant improvement in brain health, indicated by a decrease of 2.9 and 5.6 years in adjusted delta age at 12 and 24 months following bariatric surgery compared to baseline (\(p\)-value < 0.0005 for both). While the overall effect seemed to be driven by a global change across all brain regions and not from a specific region, our exploratory analysis showed lower delta age in certain brain regions (mainly in somatomotor, visual, and ventral attention networks) at 24 months. This reduced age was also associated with post-surgery improvements in BMI, systolic/diastolic blood pressure, and HOMA-IR (\(T\)-value\textsubscript{BMI} = 4.29, \(T\)-value\textsubscript{BP} = 4.67, \(T\)-value\textsubscript{HOMA-IR} = 4.12, \(T\)-value\textsubscript{HOMA-IR} = 3.16, all \(p\)-values < 0.05). In conclusion, these results suggest that obesity-related brain health abnormalities (as measured by delta age) might be reversed by bariatric surgery-induced weight loss and widespread improvements in cardiometabolic alterations.

1. Introduction

The human brain experiences morphological changes across the adult lifespan that are generally associated with a decline in cognitive performance as well as other behavioural and motor symptoms (Raz, 2009; Aboud et al., 2019; Nadig et al., 2021). The inter-individual variability in age-associated brain changes has been related to clinical outcomes (e.g. cognitive impairment and dementia), and the predicted age based on such brain changes can be used as a measure of brain health (Cole and Franke, 2017). More specifically, the difference between brain age predicted based on features derived from magnetic resonance images (named brain age hereafter) and chronological age is defined as delta age or brain age gap estimate (Zeighami and Evans, 2021). This delta age provides a measure of whether an individual’s brain appears older or younger than a normal age-matched brain (Cole and Franke, 2017; Franke et al., 2010).

Previous studies have demonstrated increases in brain age in various disorders, such as in individuals with mild cognitive impairment progressing to Alzheimer’s dementia (Franke and Gaser, 2012; Gaser et al., 2013), schizophrenia (Koutsouleris et al., 2014; Schnack et al., 2016), HIV (J.H. Cole et al., 2017), epilepsy (Pardoe et al., 2017), Down’s

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https://doi.org/10.1016/j.neuroimage.2022.119415.

Received 10 December 2021; Received in revised form 17 June 2022; Accepted 23 June 2022

Available online 24 June 2022.

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syndrome (J.H. Cole et al., 2017), major depressive disorder (Han et al., 2020), and diabetes (Franke et al., 2013). Brain age can also reliably predict cognitive impairment (Liem et al., 2017; Boyle et al., 2021), future cognitive decline and dementia (Gaser et al., 2013), and mortality (Cole et al., 2018). Moreover, brain age has been identified as a better predictor of cognitive impairment compared to chronological age (Habes et al., 2021).

A number of brain imaging studies have also reported that individuals who are overweight or obese tend to have increased brain age (Kolenic et al., 2018; Ronan et al., 2016), reflecting poorer brain health likely due to grey and white matter atrophy related to obesity (Zeighami et al., 2021; Daoust et al., 2021; Michaud et al., 2020; Garcia-Garcia et al., 2021). Interestingly, grey matter reductions associated with obesity are consistent with age-related grey matter atrophy patterns (Franz et al., 2019), highlighting the importance of obesity prevention in promoting healthy ageing. There is an increasing number of studies suggesting that at least part of the structural grey and white matter abnormalities associated with obesity might be driven by an abdominal obesity-related cardiometabolic alterations, such as inflammation, insulin resistance, dyslipidemia, and hypertension (Morys et al., 2021; Prats-Soteras et al., 2020; Guillomet-Legris and Muccioli, 2017; Moreno-Navarrete et al., 2017). Intriguingly, recent discoveries from human studies reported that cardiometabolic risk factors, including high blood pressure, markers of liver and kidney dysfunctions, diabetes, dyslipidemia, history of stroke, body mass index (BMI), and smoking are associated with an older-appearing brain and accelerated brain ageing (Beck et al., 2022; de Lange et al., 2020; Franke et al., 2014).

It is unknown whether interventions targeting weight loss and cardiometabolic improvement can reduce brain age and improve brain health. Bariatric surgery represents an interesting approach to examine the impact of marked weight loss and cardiometabolic improvements on brain health in a longitudinal setting. However, studies linking bariatric surgery-induced weight loss to reduced brain age and improved brain health are lacking. Using our unique longitudinal dataset following individuals that went through significant weight loss and cardiometabolic improvement following bariatric surgery, we investigated this hypothesis. We investigated the following specific hypotheses: 1) individuals with obesity have higher brain age than individuals with normal weight, 2) brain age decreases 4, 12, and 24 months post-bariatric surgery (comparing pre- and post-surgery), and 3) the reduced brain age following bariatric surgery is associated with improvement in cardiometabolic risk factors.

2. Methods

2.1. Data

Three distinct datasets were used to: 1) train the brain age prediction model, 2) investigate whether individuals with obesity have greater brain age than individuals with normal weight, and 3) investigate whether weight loss as a result of bariatric surgery reverses the effect of obesity and lowers the brain age.

1) Training dataset

Data used to train the brain age prediction model included participants with T1-weighted MRI data available from the second stage of the Cambridge Centre for Ageing and Neuroscience (CamCAN, https://www.cam-can.org/index.php?content=dataset) dataset, described in Shafto et al. (2014) (Shafto et al., 2014) and Taylor et al. (2017) (Taylor et al., 2017). Participants were screened for neurologic- cal and psychiatric conditions and those with such underlying disorders were excluded from the study. In total, we have included data from 640 participants (324 female), with age range between 18 and 88 (and mean +/- std of 54.2 +/- 18.6 years) and average BMI of 25.8 +/- 4.6 kg/m². T1-weighted MRIs were acquired on a 3T Siemens TIM Trio, with a 32-channel head-coil using a 3D magnetization-prepared rapid gradient echo (MPRAGE) sequence (TR = 2250 ms, TE = 2.99 ms, TI = 900 ms, FA = 9 deg, field of view (FOV) = 256 x 256 x 192 mm, 1 mm³ isotropic, GRAPPA = 2, TA = 4 min 32 s). For detailed acquisition parameters see: https://camcan-archive.mrc-cbu.cam.ac.uk/dataaccess/pdfs/CAMCAN700_MR_params.pdf.

2) Independent dataset to compare brain age between individuals with obesity and individuals with normal weight

Data used to assess the predicted brain age difference between individuals with obesity and those with normal weight included an independent sample from the Human Connectome Project (HCP) (Van Essen et al., 2013; Van Essen et al., 2012). All the participants from the HCP with a BMI higher than 35 kg/m² were included in this sample. These participants (n = 46) were individually matched (1:1) for age, sex, and ethnicity with a group of HCP individuals who had a normal body weight (n = 46). Other exclusion criteria included participants with missing information on age, sex, BMI, and ethnicity. T1-weighted 3D MPRAGE sequence with 0.7 mm (Nadig et al., 2021) isotropic resolution images were acquired by the HCP investigators using a 3T MRI scanner (Siemens Skyra) equipped with a 32-channel head coil. The following parameters were used: 256 sagittal slices in a single slab, TR = 2400 ms, TE = 2.14 ms, FA = 8 deg, FOV = 224 mm, T1 = 1000 ms, Echo Spacing = 7.6 ms, voxel size = 0.7 × 0.7 × 0.7 mm (Nadig et al., 2021) (Glasser et al., 2013).

3) Bariatric surgery-induced weight loss assessment dataset

Data used for the main analyses included participants with severe obesity (mean age at baseline = 44.0 ± 9.2 years; mean BMI at baseline = 43.9 ± 4.2 kg/m²) who underwent bariatric surgery at the Institut universitaire de cardiologie et de pneumologie de Quebec-Université Laval (IUCPQ-UL). These data are part of a larger longitudinal study, which aims at investigating the determinants of metabolic recovery following three commonly performed surgical weight-loss procedures. All the patients at the preoperative clinic that fit our inclusion criteria (women or men with a BMI ≥35 kg/m² who require surgery and who meet the NIH Guidelines for bariatric surgery (Hubbard and Hall, 1991); age between 18 and 60 years) and exclusion criteria (any uncontrolled medical, surgical, neurological or psychiatric condition; liver cirrhosis or albumin deficiency; any medication that may affect the central nervous system; pregnancy; substance or alcohol abuse; previous gastric, oesophageal, brain or bariatric surgery; gastro-intestinal inflammatory diseases or gastro-intestinal ulcers; severe food allergy; and contraindications to MRI) were approached to participate in the study. In this study, we used T1-weighted MRIs of the participants/visits that were already collected (87 participants were included at baseline, 71 participants at 4 months post-surgery, 47 participants at 12 months post-surgery, and 34 participants at 24 months post-surgery, Table 1). Not all participants completed all follow-up visits due to: 1) the COVID-19 related lockdowns (n = 12), 2) technical issues with the MRI scanner (n = 2), 3) surgical complications (n = 3), 4) pregnancy (n = 1), or 5) other personal reasons (n = 2). The Research Ethics Committee of the Centre de recherche de l’UICPQ-UL approved the study. All participants provided written informed consent to participate in the study.

Most participants (n = 46) underwent a laparoscopic sleeve gastrectomy (SG), a restrictive surgery consisting of 150 to 250 cm³ vertical gastrectomy on a 34 French bougie starting 4 to 5 cm proximal to the pylorus (Caron et al., 2017). Laparoscopic bilipancreatic derivation with duodenal switch (BPD-DS) was performed in 12 participants, which is a mixed-surgery combining restrictive and malabsorptive mechanisms by creating a 150 to 250 cm³ vertical SG and duodeno-ileal anastomosis 100 cm from ileocecal valve (Marco et al., 1993). Thirteen participants underwent a laparoscopic Roux-en-Y gastric bypass (RYGB) surgery in which proximal gastric pouch of 30–50 cm³ is created and anastomosed to the proximal small bowel by bypassing the first 100 cm and bringing a 100 cm alimentary limb on the gastric pouch.

The study design has been described in detail in Michaud et al. 202034. Briefly, approximately 2 months prior to surgery, as well as 4, 12, and 24 months post-surgery, participants underwent a physi-
Table 1: Characteristics of participants at baseline as well as 4, 12, and 24 months after bariatric surgery.

| Variable                        | Baseline | 4 months | 12 months | 24 months | p value |
|---------------------------------|----------|----------|-----------|-----------|---------|
| N                               | 87       | 71       | 47        | 34        |         |
| Sex (F:M)                       | 65:22    | 55:16    | 37:10     | 25:9      | 0.926   |
| Surgery type (SG-RYG/BPD-DS)    |          |          |           |           |         |
| -                               |          |          |           |           |         |
| Type 2 Diabetes Mellitus (Y:NY) | 21:66    |          |           |           |         |
| Age (years)                     | 44.0 ± 9.2 | 45.0 ± 8.8 | 46.3 ± 9.1 | 49.1 ± 7.5 | 0.034   |
| Weight (kg)                     | 121.7 ± 14.7 | 94.7 ± 11.6 | 81.3 ± 13.1 | 81.2 ± 14.6 | <0.001 |
| BMI (kg/m²)                     | 43.9 ± 4.2 | 34.2 ± 3.6 | 29.5 ± 4.5 | 29.0 ± 4.0 | <0.001 |
| Waist circumference (cm)        | 130.2 ± 10.4 | 110.3 ± 10.0 | 100.1 ± 11.9 | 98.5 ± 11.2 | <0.001 |
| Hip circumference (cm)          | 132.7 ± 10.8 | 114.8 ± 9.5 | 105.6 ± 9.6 | 106.0 ± 10.8 | <0.001 |
| Neck circumference (cm)         | 41.3 ± 3.5 | 37.0 ± 2.8 | 35.2 ± 3.3 | 34.8 ± 3.2 | <0.001 |
| Excess weight (%)               |          |          |           |           |         |
| Total weight (%)                |          |          |           |           |         |
| Waist (%)                       |          |          |           |           |         |
| Excess (%)                      |          |          |           |           |         |
| Systolic blood pressure (mmHg)  | 134 ± 15 | 121 ± 13 | 119 ± 16 | 116 ± 13 | <0.001 |
| Diastolic blood pressure (mmHg) | 80 ± 11 | 74 ± 10 | 72 ± 11 | 69 ± 9 | <0.001 |
| Fasting glycemia (mmol/L)       | 6.2 ± 1.6 | 5.1 ± 0.9 | 4.8 ± 0.7 | 5.0 ± 0.8 | <0.001 |
| Fasting insulin (pmol/L)        | 169.5 ± 94.1 | 65.5 ± 40.2 | 46.3 ± 34.3 | 43.7 ± 21.5 | <0.001 |
| HOMA-IR index                   | 8.1 ± 5.4 | 2.0 ± 1.1 | 1.7 ± 1.4 | 1.7 ± 0.9 | <0.001 |
| Total cholesterol (mmol/L)      | 4.5 ± 1.0 | 4.0 ± 1.1 | 4.2 ± 0.9 | 4.3 ± 0.8 | 0.005 |
| LDL-cholesterol (mmol/L)        | 2.6 ± 0.8 | 2.3 ± 1.1 | 2.3 ± 0.8 | 2.3 ± 0.7 | 0.219 |
| HDL-cholesterol (mmol/L)        | 1.2 ± 0.3 | 1.2 ± 0.3 | 1.4 ± 0.3 | 1.5 ± 0.3 | <0.001 |
| Triglycerides (mmol/L)          | 1.6 ± 0.8 | 1.4 ± 0.8 | 1.1 ± 0.5 | 1.0 ± 0.5 | <0.001 |

Results are presented as mean ± SD; repeated-measures ANOVA by linear model (Chi-square for categorical variables) comparing baseline, 4 months, 12 months, and 24 months post-surgery sessions. SG, sleeve gastrectomy; RYG, Roux-en-Y gastric bypass; BPD-DS, bilipancreatic derivation with duodenal switch; BMI, body mass index; HOMA-IR, homeostatic model assessment for insulin resistance; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

2.2. Voxel-based morphometry

Grey matter density across cortical and subcortical regions as measured by voxel-based morphometry (VBM) were used to train the brain age prediction model and assess the relationship between predicted brain age, obesity, and weight loss. Briefly, all T1-weighted structural scans were processed through a standard VBM pipeline using the following steps: 1) image denoising (Coupe et al., 2008); 2) intensity non-uniformity correction (Sled et al., 1998); and 3) image intensity normalization into range (0-100) using histogram matching. Using the ANIMAL software (Collins et al., 1994), the T1-weighted images were segmented into grey matter, white matter, and cerebrospinal fluid images. VBM analysis was performed using MNI MINC tools to generate grey matter density maps per voxel. Images were then first linearly (using a nine-parameter rigid registration) and then non-linearly registered to an average brain template (MNI ICBM152-2009c) using MNI MINC tools (http://www.bic.mni.mcgill.ca/ServicesSoftware/MINC) and Advanced Normalization Tools (ANTS) software (http://stnava.github.io/ANTs/), respectively.

2.3. Parcellation used for regularization and exploratory analysis

For cortical regions, Schaffer functional MRI parcellation at 1000 regions (Schaefer et al., 2018) was used to extract mean regional VBM values from each map. For subcortical regions, we used the atlas developed by Xiao et al. (Xiao et al., 2019), including 11 subcortical regions in each hemisphere (http://nist.mni.mcgill.ca/?p=1209).

2.4. Brain age prediction model based on the training dataset

We used principal component analysis (PCA) as the dimension reduction method to extract VBM-based brain measures for the prediction models. PCA is a singular value decomposition based data factorization method commonly used in brain age prediction studies (Smith et al., 2020; Smith et al., 2019; Franke and Gaser, 2019). We used linear regression as the main prediction model to predict the brain age, using VBM-based PCAs as predictive features. 10-fold cross validation was used to ensure generalizability of the model and avoid overfitting. We used the prediction accuracy based on the 10-fold cross validation to assess the performance of the model in the training sample (i.e. Cam-CAN dataset) and select the optimal number of features included in the final model. Root-mean-squared error (RMSE) was used as the natural cost function for the linear regression model. Furthermore, all the analyses were repeated using the linear regression model with least absolute
shrinkage and selection operator (LASSO) regularization to ensure robustness based on regional VBM values. The LASSO algorithm was used as implemented in fitlinear and lasso functions in MATLAB 2021a.

2.5. Delta age and adjusted delta age

After predicting the brain age as explained above, we calculated the difference between the predicted brain age and the chronological age (i.e. delta age). Delta age can be used as an estimate of brain-related health, since it measures the discrepancy between brain age based on the grey matter density and the expected brain age (chronological age).

\[ Y = X \times \beta_1 - \delta_1 \rightarrow \delta_1 = X \times \beta_1 - Y \] (1)

In formula (1), \( \beta_1 \), \( \delta_1 \), \( X \), and \( Y \) indicate weights estimated by the model, delta age, VBM-based principal components, and chronological age, respectively. Due to its definition, delta age is correlated with the chronological age of the participants, which by nature will act as a confounder in the analysis and will make it difficult to distinguish the effect of chronological age and the additional biological delta age. There have been several different adjustments proposed to correct for this effect (Smith et al., 2019; Le et al., 2018; Liang et al., 2019; Behehshti et al., 2019), here we use the Smith et al. (2019) definition, regressing out the portion of delta age explained by chronological age (formula (2)). We call the residual, the adjusted delta age.

\[ \delta_2 = \delta_1 - Y \times \beta_2 \] (2)

In formula (2), \( \delta_2 \) and \( \beta_2 \) indicate adjusted delta age and weights estimated by the model, respectively. Adjusted delta age has been used as the main measure of interest in the manuscript.

2.6. Statistical analyses

2.6.1. Independent sample analysis

Based on the trained models, brain age was predicted for the participants from the HCP dataset using the full sample model trained on the CamCAN dataset. We then calculated the adjusted delta age for the test sample based on age matched training sample and test set and performed unpaired t-tests to compare predicted brain age values for individuals with obesity versus individuals with normal weight.

2.6.2. Bariatric surgery-induced weight loss and brain age

Using the full-sample model trained on CamCAN dataset, brain age was predicted for the bariatric study participants prior to surgery (baseline), as well as 4 months, 12 months, and 24 months post-surgery. As explained above, we calculated the delta age and adjusted delta age with bias correction for the bariatric sample. We used a mixed effects model (model I) to examine the effect of visits on adjusted delta age, controlling for sex, age, BMI, and diabetic status at baseline as well as the surgery type and with subjects as categorical random effects.

**model I**: Adjusted Delta age \( \sim \) Visit + Age\textsubscript{baseline} + Sex + BMI\textsubscript{baseline} + Diabetic status\textsubscript{baseline} + Surgery type + (1|Subject)

2.6.3. Associations between changes in cardiometabolic risk factors following surgery and delta age

To examine the association between the changes in cardiometabolic variables and delta brain age, we used a mixed effects model (model II) with adjusted delta age as the dependant variable and the cardiometabolic variables as the fixed effects of interest, while controlling for BMI, diabetic status and age at baseline, sex, and surgery type, and including subject as a categorical random effect.

**model II**: Adjusted Delta age \( \sim \) Cardiometabolic variable + Age\textsubscript{baseline} + Sex + BMI\textsubscript{baseline} + Diabetic status\textsubscript{baseline} + Surgery type + (1|Subject)

Note that the variable named “Cardiometabolic variable” in model II reflects the longitudinal measurements of each cardiometabolic variable, collected and entered for all longitudinal timepoints. Due to the limited sample size and the multi-collinearity, the effect of each cardiometabolic variable was examined separately. Metabolic variables in this analysis included BMI, systolic/diastolic blood pressure, plasmatic levels of triglycerides, LDL-cholesterol, HDL-cholesterol and glucose, as well as the HOMA-IR. The results were corrected for multiple comparisons using Bonferroni method with a significance threshold of 0.05.

2.6.4. Exploratory regional analysis

In order to investigate the variability in delta age across brain regions, we used a parcellation-based approach to measure grey matter VBM values across the brain. We used these regional VBM values as predictors and performed a similar prediction-based analysis with each single brain region. We then calculated the adjusted delta age at baseline and across the 4, 12, and 24 months after surgery and compared the adjusted delta age post- and pre-surgery using paired t-tests. The results were corrected for multiple comparisons using False Discovery Rate (FDR) controlling method with a significance threshold of 0.05. While single-region prediction is more interpretable and targets regional specificity of the effect, the prediction accuracy is much lower at this level and the analysis should be treated as exploratory and the results should be interpreted with caution.

All prediction and statistical analyses were performed using MATLAB 2021a.

3. Results

3.1. Brain age prediction model

The linear regression model with principal components of the grey matter VBM was able to predict chronological age, yielding a cross-validated RMSE value of 8.8 (52% increase compared to mean) and correlation of \( r = 0.90 \) (p<0.0001). We used RMSE as the cost function for age prediction and evaluated the model based on the number of principal components included (for the training dataset), obtained through 10-fold cross validation. We chose the number of principal components resulting in the minimum RMSE (\( N = 45 \)) as the optimal number of the principal components, and therefore the predictive models are based on 45 VBM-based principal components as the predictive features (see Supplementary figures for the PCs with the highest model weights). These principal components are projected to the out of sample datasets (i.e. HCP and Bariatric surgery datasets) to calculate the features for the analyses. While the results obtained from regional analysis using LASSO was similar, the overall performance of the model was considerably worse (cross-validated RMSE 9.7 years) and therefore all the results are reported based on the voxel-based models.

3.2. Obesity and brain age

**Fig. 1** shows boxplots of adjusted delta age for matched individuals with obesity and individuals with normal weight from the HCP dataset. Participants living with obesity had significantly higher delta age values reflecting poorer brain health than the matched participants with normal weight (T-value = 7.08, p-value < 0.0001).

3.3. Weight loss and brain age

In order to ensure that the decrease in delta age is not sensitive to the effect of attrition, we performed our analysis with participants that had completed all 4 visits (\( N = 32 \)) as well as all participants with all available datapoints. Table S.1 in the supplementary materials compares the baseline demographic and clinical measurements between the participants that completed the 4 visits (completers) and those that did not (non-completers). Surprisingly, the completers tended to have worse baseline conditions for most variables, and these differences reached a significance level for age, systolic, and diastolic blood pressure levels.
(uncorrected p value <0.05); i.e. the completers were older, and had higher blood pressure at baseline than the non-completers. We therefore performed the analyses using both only the completers as well as all the participant data to ensure that these differences do not impact the study results and obtained similar findings. Fig. 2A shows boxplots of adjusted delta age predicted based on the MRIs acquired at baseline as well as the three visits post-surgery for participants that had completed all 4 visits. We found a significant effect of visits using a mixed effects model (model I). The results of the mixed effect model showed significant decreases in delta age 12-month post-surgery ($\beta = -2.94 \pm 0.8$, T stat = $-3.66$, p-value < 0.0005) and 24-month post-surgery visits compared to baseline ($\beta = -4.5 \pm 0.8$, T stat = $-5.58$, p-value < 0.0001), but not at 4-month post-surgery ($\beta = 0.37 \pm 0.8$, T stat = 0.46, p-value = 0.64) compared to baseline. The complete tables reporting all the estimated parameters and their corresponding statistics are included in the supplementary materials (Tables S.2). Fig. 2B shows boxplots of adjusted delta age predicted based on the MRIs acquired at baseline (the visit prior to surgery) as well as the three visits (4 months, 12 months, and
24 months) post-surgery for all the participants. Similarly, we found a significant effect of visits using a mixed effects model controlling for sex, age, and BMI at baseline as well as the surgery type (model I). The results of the mixed effect model showed significant decreases in delta age 12-month post-surgery (\( \beta = -2.42 \pm 0.64, T\)-value\( = -3.76, p\)-value\( < 0.0005\)) and 24-month post-surgery visits compared to baseline (\( \beta = -4.67 \pm 0.72, T\)-value\( = -6.40, p\)-value\( < 0.0005\)), but not at 4-month post-surgery (\( \beta = -0.14 \pm 0.55, T\)-value\( = -0.25, p\)-value\( = 0.79\)) compared to baseline. The complete tables reporting all the estimated parameters and their corresponding statistics are included in the supplementary materials (Tables S.3).

### 3.4. Associations between Delta brain age and cardiometabolic risk factors

We used mixed effect models (model II) to examine the associations between the delta brain age and adiposity/cardiometaabolic factors including BMI, systolic/diastolic blood pressure, plasmatic levels of triglycerides, LDL-cholesterol, HDL-cholesterol, and glucose as well as the HOMA-IR. For participants that had completed all 4 visits (\( N = 32\)), we found a significant association between adjusted delta age and BMI, systolic blood pressure as well as diastolic blood pressure, and HDL-cholesterol (\( T\)-value\( _{BMI} = 4.4, T\)-value\( _{SBP} = 4.15, T\)-value\( _{DBP} = 4.14, T\)-value\( _{HDL} = -3.2 \) respectively, all Bonferroni corrected \( p\)-values \( < 0.05\)) where higher BMI and blood pressure and lower HDL-cholesterol was related to higher delta age. The association between adjusted delta age and HOMA-IR and LDL-cholesterol did not survive the Bonferroni correction for multiple comparison (Tables S.2, sheets 2–5). Repeating the analysis in the sample with all participants, we found a significant association between adjusted delta age and BMI, systolic/diastolic blood pressure, and HOMA-IR (\( T\)-value\( _{BMI} = 4.29, T\)-value\( _{SBP} = 4.67, T\)-value\( _{DBP} = 4.12, T\)-value\( _{HOMA-IR} = 3.16 \) respectively, all Bonferroni corrected \( p\)-values \( < 0.05\)) where higher BMI, blood pressure, and HOMA-IR was related to higher delta age. The complete tables reporting the estimated parameters and their corresponding statistics are included in the supplementary materials (Tables S.3, sheets 2–5). We did not find any significant association between adjusted delta age and the rest of cardiometabolic variables in the complete sample.

### 3.5. Exploratory regional analysis

While the predictive model based on PCA provides a global perspective of brain age and health, we cannot specify the brain regions contributing to overall differences. In order to identify variability across brain regions, we used a parcellation-based approach with VBM values as predictive features. We repeated the age prediction and brain age calculation using one brain region in each model. While as expected, the model performance is much lower (as measured by RMSE) than whole brain analysis, this exploratory analysis provides some regional insights. Fig. 3 shows the brain regions with significantly lower adjusted delta age at 24 months post-surgery compared to baseline mainly in somatomotor, visual, and ventral attention networks. We did not find any significant differences at single region level at 4 months and 12 months post-surgery.

### 4. Discussion

In this study, we assessed the impact of weight loss and cardiometabolic improvement following bariatric surgery on brain health, as measured by change in brain age estimated based on VBM measurements. Using an independent dataset from HCP, we found a higher brain age for individuals with obesity compared to individuals with normal weight. Our results also showed significant improvement in brain health, indicated by a decrease of 2.9 and 5.6 years in adjusted delta age at 12 and 24 months following bariatric surgery as compared to baseline. While the overall effect seemed to be driven by a global change across all brain regions and not from a specific region, our exploratory analysis showed lower delta age in certain brain regions (mainly in somatomotor, visual, and ventral attention networks) at 24-month. This reduced age was also associated with post-surgery improvements in BMI, systolic/diastolic blood pressure, and HOMA-IR.

Our results based on the participants from the HCP study are in line with previous studies in the literature indicating associations between obesity and poorer brain health as reflected in higher delta age in individuals with obesity compared to those with normal weight. In 234 participants, Kolenic et al. (Kolenic et al., 2018) found a significant and positive association between BMI and brain age scores. Smith et al. also reported a strong relationship between BMI and brain age assessed with multimodal imaging for 19,038 participants from the UK Biobank (Smith et al., 2019). Waist-to-hip ratio was also associated with delta age calculated based on DTI data (Beck et al., 2022). In a cross-sectional study, overweight and obesity was associated with an estimated 10-year increase in brain age based on white matter volume (Ronan et al., 2016). These brain age differences are likely due to grey matter and white matter atrophy in individuals with obesity (García-García et al., 2019). It has been suggested that part of these structural brain alterations observed in obesity might be attributed to the cardiometabolic burden that abdominal adiposity entails (García-García et al., 2019). For instance, chronic low-grade inflammation related to abdominal obesity has been associated with disruptions in grey and white matter integrity as well as cerebrovascular disease (Moreno-Navarrete et al., 2017; Alfaro et al., 2018; Verstynen et al., 2013). A recent large-scale study from the UK Biobank cohort (~20 000 participants) found that inflammation, hypertension, and type 2 diabetes are associated with brain small vessel disease (as measured by volume of white matter hyperintensities), which is in turn related to changes in brain cortical and subcortical morphology. These changes also appear to be linked to poorer cognitive performance (Morys et al., 2021). The obesity-related cardiometabolic alterations might lead to negative effects on brain health by disrupting cerebral blood flow and its supply (García-García et al., 2019). A few recent large-scale studies have also reported positive associations between delta age and cardiometabolic risk factors, including blood pressure, smoking, alcohol intake, and stroke risk (Beck et al., 2022; de Lange et al., 2020). These cardiometabolic risk factors can contribute to the development of atherosclerosis, leading to cerebral ischaemia, microstructural damage, and cognitive impairment (Wardlaw et al., 2019). Taken together, these findings are in favour of the hypothesis that obesity-related cardiometabolic alterations might lead to cerebral grey and white matter abnormalities and poorer brain health.

Comparing delta age values prior to and after bariatric surgery showed a steady improvement in brain health, as reflected in significant decrease in delta age values at 12 months and 24 months post-surgery. These results are in line with previous MRI studies from our group (Zeighami et al., 2021; Daoust et al., 2021; Michaud et al., 2020) and others (Tuuliri et al., 2016; Rullmann et al., 2018; Zhang et al., 2016) showing widespread increases in white matter and grey matter densities as well as resting neural activity (as measured by fractional-amplitude of low frequency fluctuations) following bariatric surgery, suggesting a global effect of surgery on brain status. These grey matter density increases were more pronounced and widespread 12 months post-surgery compared to 4 months post-surgery (Michaud et al., 2020), which could explain why the delta age values at 4 months post-surgery were similar to baseline levels. The amount of weight loss and the improvement in cardiometabolic factors were also less significant 4 months post-surgery compared to 12- and 24-months post-surgery. The improvement in brain age following the surgery is also in line with several studies showing a delay or a slowing of ageing processes with caloric restriction and/or weight loss (Colman et al., 2014; Masoro, 2005).

Decrease in delta age values following bariatric surgery was significantly associated with the degree of weight loss and concomitant improvement in cardiometabolic factors, more specifically blood pressure and insulin resistance. However, no significant association was ob-
served with changes in LDL-cholesterol or triglycerides levels. This is consistent with the study from Kolenic et al. that did not find significant associations between delta age and lipid profiles (Kolenic et al., 2018). Our results are also consistent with our previous findings showing that the increase in grey matter and white matter densities after bariatric surgery are correlated with weight loss and improvement of the metabolic/inflammatory profiles (Michaud et al., 2020). Together, these findings support the idea that the improvement in brain integrity and health, as indexed by delta age, could be a consequence of a better cerebral blood flow and improved insulin sensitivity after bariatric surgery-induced weight loss. Recent meta-analyses provide strong evidence that bariatric surgery is associated with improvement in subclinical atherosclerosis, artery endothelial function, and resolution of hypertension (Lupoli et al., 2016; Wilhelm et al., 2014). These cardiometabolic/vascular changes observed following bariatric surgery may lead to improved angiogenesis and changes in synaptic connectivity, dendritic branching, axon sprouting, and glial cells, which could influence grey matter density as well as brain health (Zatorre et al., 2012; Tardif et al., 2017). Furthermore, individuals with obesity might have a different molecular and lipid brain profile at microstructural level which might impact the regional neuroanatomical signal. These potential alterations can partially explain the higher brain age in participants with obesity as well as the potential mechanism that underlies the recovery after the bariatric surgery. Future studies are needed to better understand the underlying mechanisms through which the cardiometabolic improvements following bariatric surgery influence brain integrity and brain health.

While the chronological age ranges are different across the datasets, in the case of CamCAN, we have trained our model using a lifespan dataset including participants with chronological ages ranging from 18 to 88 years old, which will ensure that the model is able to capture the biological age of the participants from bariatric surgery, with a wide margin outside their chronological age. We used brain age as proxy measure for improved brain health since we didn’t have access to the direct measures of brain health (e.g. cerebrospinal fluid measures). However these measures have been reported to be associated with brain age (Gaser et al., 2013; Cole et al., 2018). $\beta$-$\gamma$ is the prediction error, which is a combination of errors from different sources including individual variability, biological age differences, the model, and noise (systematic and random noise). If what we measure as brain age was random noise, the study of brain age would not have been helpful to answer any biological question. However, given the wealth of studies that have demonstrated a reliable relationship between the delta age and other biological and health variables (Cole and Franke, 2017; Franke and Gaser, 2019), we believe that delta brain age reflects a systematic biological signal.

Some limitations should be addressed. We did not control for some factors associated with brain ageing such as smoking, alcohol consumption, education, and physical activity levels (Wrigglesworth et al., 2021). Furthermore, the bariatric population normally includes a lower proportion of men (approximately 30%), and we recruited a similar proportion of men (approximately 25%) in the current study. Despite previous reports of sex-specific differences in brain ageing and cardiometabolic factors (Franke et al., 2014), due to sample size limitations, we were unable to explore changes in men and women separately. Similarly, due to the limited sample size diminishing the statistical power of our models, we did not investigate any potential interactions (such as time:cardiovascular measures) in the models. Future studies with larger sample sizes and sufficient statistical power are warranted to investigate these associations. Further, the current sample mostly included individuals that went under sleeve gastrectomy surgery. Due to the smaller sample sizes of the other two surgery groups (RYGB and DBP), we were unable to compare the different surgical interventions, and only included surgery type as covariate in our models for the current analyses. In future, when we have sufficiently large sample sizes from each surgery type, it would be interesting to examine whether there are differences in the consequences of restrictive versus malabsorptive bariatric procedures on brain structure.
The participants’ body size as well as their changes can potentially affect the MRI field and its homogeneity and consequently result in change of the MRI signals. This is a potential confound for all studies targeting brain correlates and alteration in individuals with obesity, and the direction and degree of these alterations and whether they can be sufficiently corrected by standard inhomogeneity correction methods need future investigation that directly targets these effects. Another limitation is the fact that the T1-weighted MRIs in CamCAN and HCP dataset were acquired using 3T Siemens MRI scanner, while the T1-weighted MRIs in bariatric surgery dataset were acquired with a 3T Philips MRI scanner. While the image processing pipelines used in the current study have been developed and extensively validated for use in multi-centre and multi-scanner datasets and are designed to minimize such potential differences (M. Dadar et al., 2020; Dadar et al., 2022; M. Dadar et al., 2020; Dadar et al., 2018; M. Dadar et al., 2020), the use of different scanners might have affected the reliability and robustness of the prediction model, and future studies investigating the impact of scanner model and manufacturer are warranted to demonstrate such potential effects.

Model II does not include visit # as a covariate and only includes one cardiometabolic variable at a time. Since the intervention results in weight loss over two years, accompanied by improvement in most of the variables, all our cardiometabolic variables and time are correlated longitudinally. Time in this case has a dominant effect and can explain a high degree of variance in most of the brain and cardiometabolic variables. That said, time is not the causal mechanism here, it is the surgery that over time results in weight loss and change in cardiometabolic variables which are the most likely causes of brain age improvement. Distinguishing these effects over time needs a degree of control that is only possible in animal trials.

The brain age prediction model had an RMSE of 8.7 (for 18.61 years standard deviation of age), comparable to what has been previously observed in the literature, and using the same dataset (Zeighami and Evans, 2021; Ronan et al., 2016). A 10-fold cross validation scheme was used to ensure that the results were not impacted by leakage (Mateos-Pérez et al., 2018). The same training dataset used here has been used in the study by Ronan et al. (Ronan et al., 2016) However, to assess the impact of obesity on delta age, we used an age-matched independent sample from HCP, to ensure that the findings are not biased by the fact that older people in general tend to be more overweight and obese.

In conclusion, our study revealed significant obesity-related differences in brain health (as measured by delta age) between individuals with obesity and those with normal weight, as well as a marked improvement in brain age following bariatric surgery. These results suggest that obesity-related brain health abnormalities might be reversed by means of significant and sustained weight-loss, along with widespread improvements in cardiometabolic alterations.

Declaration of Competing Interest

A. T. and L. B. are recipients of research grant support from Johnson & Johnson Medical Companies and Medtronic for studies on bariatric surgery and the Research Chair in Bariatric and Metabolic Surgery at IUCPQ and Laval University. AT has received consulting fees from Bausch Health, Novo Nordisk and acts as a consultant for Biotwin. No author declared a conflict of interest relevant to the content of the manuscript.

Credit authorship contribution statement

Yashar Zeighami: Conceptualization, Methodology, Formal analysis, Writing – original draft. Mahsa Dadar: Conceptualization, Formal analysis, Writing – review & editing. Justine Daoust: Investigation, Formal analysis, Writing – review & editing. Mélissa Pelletier: Investigation, Writing – review & editing. Laurent Biertho: Funding acquisition, Resources, Writing – review & editing. Léonie Bouvet-Bouchard: Resources, Writing – review & editing. Stephanie Fulton: Funding acquisition, Writing – review & editing. André Tchernof: Funding acquisition, Writing – review & editing. Alain Dagher: Funding acquisition, Writing – review & editing. Denis Richard: Funding acquisition, Writing – review & editing. Alan Evans: Supervision, Writing – review & editing. Andréeane Michaud: Conceptualization, Investigation, Writing – original draft, Supervision.

Acknowledgments

We would like to acknowledge the contribution of surgeons, nurses, the medical team of the bariatric surgery program at IUCPQ, MRI technicians, Xavier Moreel, Coordinator of the Plateforme d’imagerie avancée at IUCPQ, and Guillaume Gilbert, MR Clinical Scientist, Philips Canada as well as the collaboration of participants. Data collection for training dataset was provided by the Cambridge Centre for Ageing and Neuroscience (CamCAN), CamCAN funding was provided by the UK Biotechnology and Biological Sciences Research Council (grant number BB/H008217/1), together with support from the UK Medical Research Council and University of Cambridge, UK. HCP data was obtained from the Human Connectome Project, WU-Minn Consortium (Principal Investigators: David Van Essen and Kamil Ugurbil; 1U54MH091657) funded by the 16 NIH Institutes and Centers that support the NIH Blueprint for Neuroscience Research; and by the McDonnell Centre for Systems Neuroscience at Washington University. Authors thank Compute Canada (https://www.computecanada.ca/home) for the usage of the computing resources in the current work.

Funding

This study is supported by a Team grant from the Canadian Institutes of Health Research (CIHR) on bariatric care (TB2-138776) and an Investigator-initiated study grant from Johnson & Johnson Medical Companies (Grant ETH-14-610). Funding sources for the trial had no role in the design, conduct or management of the study, in data collection, analysis or interpretation of data, or in the preparation of the present manuscript and decision to publish. This research was undertaken thanks in part to funding from the Canada First Research Excellence Fund, awarded to McGill University for the Healthy Brains, Healthy Lives (HBHL) initiative. Dr. Zeighami reports receiving research funding from the Healthy Brains for Healthy Lives (Grant HBHL-2b-NISU-19). Dr. Dadar reports receiving research funding from the Healthy Brains for Healthy Lives (Grant HBHL-2b-NISU-18), Alzheimer Society Research Program (ASRP), and Douglas Research Centre (DRC). The co-investigators and collaborators of the REMISSON study are (alphabetical order): Bégin C, Biertho L, Bouvier M, Biron S, Cani P, Carpenter A, Dagher A, Dubé F, Ferguson A, Fulton S, Hould FS, Julien F, Kieffer T, Laferrière B, Lafontaine A, Lebel S, Lescelleur O, Levy E, Marette A, Marceau S, Michaud A, Picard F, Poirier P, Richard D, Schertzer J, Tchernof A, Vohl MC.

Code data availability statement

The data and the scripts will be made available upon reasonable request.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.neuroimage.2022.119415.

References

Aboud, K.S., et al., 2019. Structural covariance across the lifespan: brain development and aging through the lens of inter-network relationships. Hum. Brain Mapp. 40, 125–136.
Alfaro, F.J., et al., 2018. White matter microstructure and cognitive decline in metabolic syndrome: a review of diffusion tensor imaging. Metabolism 78, 52–68.

Beck, D., et al., 2022. Cardiometabolic risk factors associated with brain age and accelerate brain aging. Hum. Brain Mapp. 43, 11379–11389.

Behshiri, I., Nugent, S., Potvin, O., Duchesne, S., 2019. Bias-adjustment in neuroimaging-based brain age frameworks: a robust scheme. NeuroImage: Clinical 24, 102663.

Biertho, L., et al., 2010. Is bilateral pialarion diversion with duodenal switch indicated for patients with body mass index <50kg/m² Surgery. Relat. Dis. J. 6, 508–514.

Boyle, R., et al., 2021. Brain-predicted age difference score is related to specific cognitive functions: a multi-site replication analysis. Brain Imaging Behav 15, 327–345.

Caron, M., et al., 2017. Long-term nutritional impact of sleeve gastrectomy. Surg. Obes. Relat. Dis. 13, 164–177.

Cole, J.H., Franke, K., 2017. Predicting Age Using Neuroimaging: innovative brain Ageing Biomarkers. Trends Neurosci. 40, 681–690.

Cole, J.H., et al., 2017a. Predicting brain age with deep learning from raw imaging data resulting in a reliable and interpretable biomarker. NeuroImage: Clin. 16, 113–124.

Cole, J.H., et al., 2017b. Brain-predicted age in Down syndrome is associated with beta amyloid deposition and cognitive decline. Neurobiol. Aging 56, 41–49.

Cole, J.H., et al., 2018. Brain age predicts mortality. Mol. Psychiatry 23, 1385–1392.

Collins, D.L., Neelin, P., Peters, T.M., Evans, A.C., 1994. Automatic 3D intersubject registration of MR volumetric data in standardized Talairach space. J. Comput. Assist. Tomogr. 18, 192–205.

Colman, R.J., et al., 2014. Caloric restriction reduces age-related and all-cause mortality in rhesus monkeys. Nat. Commun. 5, 3557.

Coupe, P., et al., 2008. An optimized blockwise nonlinear means denoising filter for 3-D magnetic resonance images. IEEE Trans. Med. Imaging 27, 425–441.

Dadar, M., Fonov, V.S., Collins, D.L., 2018. & Alzheimer’s disease neuroimaging initiative. A comparison of existing and available 128 MRI stereotactic registration techiniques. NeuroImage 174, 191–200.

Dadar, M., et al., 2020a. Cerebral atrophy in amyotrophic lateral sclerosis parallels the pathological distribution of TDP43. Brain 143, 971–981.

Daducci, A., Ronchi, S., Duchesne, S., Collins, D.L., 2020b. Alzheimer’s Disease Neuromaging Initiative. The temporal relationships between white matter hyperintensities, neurodegeneration, amyloid beta, and cognition. Alzheimer’s Disease (Ams) 12, e125453.

Dadar, M., Duchesne, S., Group, C.C.N.A., Group, the CIMA-Q, 2020c. Reliability assessment of tissue classification algorithms for multi-center and multi-scanner data. NeuroImage 217, 116928.

Dadar, M., Manera, A.L., Ducharme, S., Collins, D.L., 2022. White matter hyperintensities are associated with grey matter atrophy and cognitive decline in Alzheimer’s disease and frontotemporal dementia. Neurobiol. Aging 111, 54–63.

Dauot, J., et al., 2021. White matter integrity differences in obesity: a meta-analysis of diffusion tensor imaging studies. NeuroImage: Clin. 51, Rev. 129, 133–141.

de Lange, A.-M.G., et al., 2020. Multimodal brain-age prediction and cardiovascular risk the Whitehall II MRI sub-study. NeuroImage 222, 117792.

Franke, K., Gaser, C., 2012. Longitudinal changes in individual brain age in healthy aging, mild cognitive impairment, and Alzheimer’s disease. Geropsych (Bres) 25, 235–245.

Franke, K., Ziegler, G., Klippen, S., Gaser, C., 2010. Estimating the age of healthy subjects from T1-weighted MRI scans using kernel methods: exploring the influence of various parameters. NeuroImage Neuroimage 50, 883–892.

Franke, K., Gaser, C., Manera, A.L., Novak, V., 2013. Advanced BrainAGE in older adults with type 2 diabetes mellitus. Front. Aging Neurosci 5, 90.

Franke, K., Ristow, M., Gaser, C., 2014. Gender-specific impact of personal health parameters on individual brain aging in cognitively unimpaired elderly subjects. Front. Aging Neurosci 6, 94.

Franz, C.E., et al., 2019. Body mass trajectories and cortical thickness in middle-aged men: a 42-year longitudinal study starting in young adulthood. Neurobiol. Aging 79, 11–21.

Franke, K., Gaser, C., 2019. Ten years of BrainAGE as a neuroimaging biomarker of brain aging: what insights have we gained? Front. Neurol. 10, 785.

Garcia-Garcia, I., et al., 2019. Neuroanatomical differences in obesity: meta-analytic findings and their validation in an independent dataset. Int. J. Obes. 43, 943–951.

Garcia-Garcia, I., et al., 2021. Relationship between impulsivity, uncontrolled eating and body mass index: a hierarchical model. Int. J. Obes. 1–8. doi:10.1038/s41366-021-00966-4.

Glasner, M.F., et al., 2013. The minimal preprocessing pipelines for the Human Connectome Project. NeuroImage 80, 105–124.

Guillemot-Legris, O., Muccioli, G.G., 2017. Obesity-Induced Neuroinflammation: beyond the Hypothalamus. Trends Neurol. 40, 237–253.

Haben, M., et al., 2021. The Brain Chart of Ageing: machine-learning analyses reveals links between brain aging, white matter disease, amyloid burden, and cognition in the ISTAGING consortium of 10,216 harmonized MR scans. Alzheimer’s & Dementia 17, 89–102.

Han, L.K.M., et al., 2020. Brain aging in major depressive disorder: results from the ENIGMA major depressive disorder working group. Mol. Psychiatry 1–16. doi:10.1038/s41380-020-0754-a.

Hubbard, W.S., Hall, W.H., 1991. Gastrointestinal surgery for severe obesity. Obes. Surg. 1, 257–265.

Kolenic, M., et al., 2018. Obesity, dyslipidemia and brain age in first-episode psychosis. J. Psychiatr. Res. 99, 151–158.

Kotroniaris, N., et al., 2014. Accelerated brain aging in schizophrenia and beyond: a neuroanatomical marker of psychiatric disorders. Schizophr Bull 40, 1140–1153.

Le, T.T., et al., 2018. A nonlinear simulation framework supports adjusting for age when analyzing BrainAGE. Front. Aging Neurosci. 10, 317.