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ARTICLE

Bariatric Surgery

Brain effect of bariatric surgery in people with obesity

Angela Dardano[1], Gayane Aghakhanyan[2], Carlo Moretto[3], Annamaria Ciccarone[1], Rosario Bellini[3], Veronica Sancho Bornez[1], Giovanni Ceccarini[4], Ferruccio Santini[4], Duccio Volterrani[2], Stefano Del Prato[1]✉ and Giuseppe Daniele[1]

BACKGROUND/OBJECTIVES: The link between obesity and brain function is a fascinating but still an enigmatic topic. We evaluated the effect of Roux-en-Y gastric bypass (RYGB) on peripheral glucose metabolism, insulin sensitivity, brain glucose utilization and cognitive abilities in people with obesity.

SUBJECTS/METHODS: Thirteen subjects with obesity (F/M 11/2; age 44.4 ± 9.8 years; BMI 46.1 ± 4.9 kg/m^2) underwent 75-g OGTT during a [18F]FDG dynamic brain PET/CT study at baseline and 6 months after RYGB. At the same timepoints, cognitive performance was tested with Mini Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA), Trail making test (TMT) and Token test (TT). Glucose, insulin, C-peptide, GLP-1, GIP, and VIP levels were measured during OGTT. Leptin and BDNF levels were measured before glucose ingestion.

RESULTS: RYGB resulted in significant weight loss (from 46.1 ± 4.9 to 35.3 ± 5.0 kg/m^2; $p < 0.01$ vs baseline). Insulin sensitivity improved (disposition index: from 1.1 ± 0.2 to 2.9 ± 1.1; $p = 0.02$) and cerebral glucose metabolic rate (CMRg) declined in various brain areas (all $p \leq 0.01$). MMSE and MoCA score significantly improved ($p = 0.001$ and $p = 0.002$, respectively). TMT and TT scores showed a slight improvement. A positive correlation was found between CMRg change and HOMA-IR change in the caudate nucleus ($\rho = 0.65$, $p = 0.01$). Fasting leptin decreased (from 80.4 ± 13.0 to 16.1 ± 2.4 ng/dl; $p = 0.001$) and correlated with CMRg change in the hippocampus ($\rho = 0.50$; $p = 0.008$). CMRg change was correlated with cognitive scores changes on the TMT and TT (all $p = 0.04$ or less).

CONCLUSIONS: Bariatric surgery improves CMRg directly related to a better cognitive testing result. This study highlights the potential pleiotropic effects of bariatric surgery.

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INTRODUCTION

Accumulating evidence suggests that obesity is associated with brain changes, and cognitive impairment [1]. Although research addressing links between obesity and cognitive function in young adults are limited, data indicate early cognitive decline also in young age [2]. We have recently reported a correlation between body mass index (BMI) and brain plasticity, with subjects affected by obesity failing to show the physiologic homoeostatic plasticity seen in normal-weight subjects [3]. We have also reported that altered neural plasticity is restored after bariatric surgery [4]. Multiple mechanisms can lead to brain malfunction. Obesity is characterized by chronic low-grade inflammation and increased oxidative stress which can affect vascularization and blood brain barrier integrity, exacerbate brain insulin resistance, and reduce gray matter volume [5]. Changes accompanying obesity such as insulin and leptin resistance, abnormal secretion of gut hormones, and adipokine dysregulation are likely to contribute to brain dysfunction [6]. Of interest, insulin resistance has been identified as an independent predictor of poorer performance and greater decline in verbal fluency [7].

Energy brain metabolism is likely to be involved in neuronal response to changes in body weight and cerebral glucose metabolism has been proposed as a biomarker of brain abnormalities. 18F-fluorodeoxyglucose positron emission tomography/computed tomography ([18F]FDG PET/CT) has been used to explore the effects of obesity on brain metabolism [8]. By using this approach, compared to healthy individuals, brain glucose metabolism appears to be higher in adults with obesity or with mild cognitive dysfunction [9]. Moreover, brain hypermetabolism has been found to be associated with hepatic and whole-body insulin resistance, food desire and an unfavourable balance between anticipated reward and cognitive control [9]. Perturbations of brain glucose metabolism have been reported in insulin-resistant subjects with and without type 2 diabetes [10, 11], and in young subjects at high risk for future obesity [12].

[1]Department of Clinical and Experimental Medicine, Section of Diabetes and Metabolic Diseases, University of Pisa, Nuovo Ospedale Santa Chiara, Pisa, Italy. [2]Regional Center of Nuclear Medicine, Department of Translational Research and Advanced Technologies in Medicine, University of Pisa, Nuovo Ospedale Santa Chiara, Pisa, Italy. [3]Section Bariatric Surgery Unit, Nuovo Ospedale Santa Chiara, Pisa, Italy. [4]Obesity and Lipodystrophy Center, Endocrinology Unit, University of Pisa, Nuovo Ospedale Santa Chiara, Pisa, Italy. ✉email: stefano.delprato@unipi.it

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Bariatric surgery is the most effective mean of obtaining durable weight loss in individuals affected by obesity, with benefits extending to many obesity-related comorbid conditions [13]. Weight loss after bariatric surgery has been shown to reduce brain glucose hypermetabolism [14], recover brain tissue integrity [15, 16] and improve cognitive function [17–25]. However, the underlying mechanisms are still poorly understood although changes in the hormonal setting are likely to be implicated. Impaired insulin and leptin signalling pathways in the central nervous system (CNS) are associated with impaired brain function [26], while restoration of insulin and leptin signalling attenuates neuronal damage and promotes cognition [27].

Nonetheless, to the best of our knowledge, no studies so far have sought the potential association between changes in brain glucose metabolism and cognitive function in individuals with obesity undergoing bariatric surgery. Therefore, we have designed a study to assess insulin sensitivity, brain glucose utilization and cognitive performance in subjects with obesity before and after Roux-en-Y gastric bypass (RYGB).

METHODS

Study population

Twenty subjects with obesity and without type 2 diabetes, eligible for RYGB were recruited in the study. Subjects with drugs or alcohol abuse, medications affecting brain metabolism/function or glucose levels, psychiatric illness, head injury, brain cancer, dementia, epilepsy, learning disorder, developmental disability, impaired sensory function, severe sleep disturbances or use of continuous positive airway pressure, psychotropic medications, and steroids treatment were excluded. Similarly, we excluded subjects with contraindications to [18F]FDG PET, type 1 diabetes, heart failure (NYHA III-IV), increased liver function enzymes (>2× the normal upper limit), pregnancy or pregnancy planning, evidence of any condition, therapy, laboratory abnormality, or other circumstance with an unacceptable risk to the subject or potentially interfering with study procedures. All subjects underwent a complete nutritional assessment and were advised to maintain their dietary habits throughout the study. The study - registered at ClinicalTrials.gov with the identifier NCT03414333 - was approved by the local Hospital/University Ethical Committee and carried out in accordance with the Declaration of Helsinki. Each participant provided written informed consent before entering in the study.

Study design

At baseline, all subjects reported to our metabolic and endocrine Units after an overnight fasting for medical history collection, anthropometric and blood pressure measurements, and blood sample drawing for routine lab tests. After this initial visit, all subjects underwent neuropsychological evaluation and dynamic [18F]FDG PET/CT during a standard (75 g) oral glucose load (OGTT) with sampling for the assessment of plasma glucose and hormone concentrations. Each procedure was performed at 5–7-day interval. All baseline evaluations were completed 2 weeks before subjects underwent a RYGB at the local Unit of Bariatric Surgery. Subjects were then requested to repeat baseline assessment 6 months after surgery.

Biochemical analysis

Plasma glucose concentration was measured using the glucose oxidase method (Beckman, Fullerton, CA, USA). Samples for GIP and GLP-1 were drawn in tube containing protease inhibitors, specifically optimized for stabilization of incretins (BD P800, BD Biosciences, USA). Total GLP-1 and active GLP-1 were measured by ELISA (EMD Millipore, St. Charles, Missouri, USA). Insulin and C-peptide were assessed by radioimmunoassay (IRMA, PANTEC srl Turin, Italy). GIP and VIP were measured using an enzyme immunoassay (RayBiotech, Norcross, GA, USA). Fasting leptin and BDNF levels were measured using a sandwich enzyme-linked immunosorbent assay, according to the manufacturer's specifications (RayBiotech, Norcross, GA, USA). All samples were stored at −70 C until analysis.

Neuropsychological tests

All subjects underwent assessment of cognitive performance by the administration of the Mini Mental State Examination (MMSE), the Montreal Cognitive Assessment (MoCA), the Trail Making Test (TMT) and the Token Test (TT). MMSE was used as a screening tool [28], and a score less than 24 is the generally accepted cut-off for cognitive impairment. MoCA is a brief cognitive screening tool with high sensitivity and specificity for detecting mild cognitive impairment [29] as it assesses several cognitive domains: visuospatial/executive abilities, naming, attention, language, abstraction, delayed recall, and orientation. The recommended cut-off score of 26 points was used for data analysis. TMT part A and B [30] assesses cognitive flexibility and executive functions. TMT-A consists of a series of 25 numbered circles, and participants have to connect numbers from 1 to 25 in ascending order (i.e. 1–2–3 etc.). TMT-B consists of 13 numerical numbers and 12 letters; participants are requested to connect numbers and letters in an alternating progressive sequence (i.e., 1-A-2-B, etc.) as fast and accurately as possible without lifting the pen from the worksheet. The typical TMT does not involve an explicit time constraint, but a cut-off of 300 s is typically applied for test discontinuation, with a faster speed indicating better performance. TMT-A provides a baseline measure of psychomotor speed, visuospatial search, and target-directed motor tracking, while TMT-B relies on both working memory and task-switching ability. TT was administered to assess the receptive language ability [31]. It consists of a series of coloured tokens in squared or round forms of two different sizes, and the subject is instructed to perform a series of commands, such as "touch the red circle" or "touch the small yellow square and the big red circle". TT mean normal range is 0–36 with scores between 25 and 28 indicating mild comprehension problems and 17–27 moderate problems; scores below this are classified as severe or very severe [31]. Depressive symptoms were explored using the Patient Health Questionnaire-9 (PHQ-9) [32]. The severity of the depression symptoms was categorized as follow: score of 0–4 no symptoms, 5–9 mild, 10–14 moderate, 15–19 moderately severe, and ≥20 severe symptoms. All subjects also underwent a psychological interview. All neuropsychological assessments were administered by a trained specialist (AD) in a quiet environment. Age and education level adjustments were made as appropriate. The average time to complete this battery of tests was approximately 50–60 min.

[18F]FDG PET/CT imaging acquisition and pre-processing

All patients underwent a [18F]FDG PET/CT study during a standard OGTT (75 g), using a PET/CT scanner Discovery 710 (GE Medical Systems, Milwaukee, USA). On the morning of the assessment, after at least 6 h overnight fasting, a large antecubital vein was cannulated for blood drawing for determination of metabolites and plasma radioactivity. After collection of baseline blood samples, all subjects underwent an OGTT (75 g) and, within 5 min after glucose ingestion, 3 MBq/kg of [18F]FDG were injected through a vein of the contralateral arm. A dynamic PET imaging (60 min) started for the acquisition in three-dimensional mode and venous blood samples were drawn at 5, 10, 15, 30, 45, 60, 65, 70, 75, 80, 85, 90, 105, 120 min for plasma radioactivity. Low-dose CT was acquired before PET for attenuation correction of PET imaging.

Calculations

Kinetic modelling and parametric image creation. The software package PMOD (PMOD Technologies Ltd, Zürich, Switzerland) was used for PET data kinetic modelling. An image-derived arterial input function was obtained by manually defining two separate volumes of interest (VOI) on the carotid arteries over the first pass of FDG. The regional time activity curve within each carotid artery was generated as the time sequence of the averaged VOI values [33]. To correct for the spillover between the carotid artery and the surrounding tissue, a tissue time activity curve was generated from a VOI automatically drawn by dilatating the carotid artery VOI for 2 mm. Then, later time (30–120 min) venous samples, were used for the spillover and partial volume correction by non-negative least squares method, according to the method described by Chen et al. [33]. The Patlak graphical plot method for two-tissue compartment was used to calculate the net uptake rate for FDG (Ki). A correction of the Patlak plot for glucose changes has been applied according to the following formula published by Dunn et al. [34]:

$$\frac{F_T(t)}{F_p(t)} = K_i' \frac{\int_0^t (G_p(t=0)/G_p(t)) F_p(T) dT}{F_p(t)}$$

The integral has been calculated by fitting plasma glucose curve overtime and applying point-by-point the ratio $G_p(t=0)/G_p(t)$ to the $F_{p(T)}$ curves.

After the correction of *K*'i for changes of plasma glucose, CMRg was at last calculated as follows:

$$_{\mathrm{CMRg}} = \frac{K_i' G_p(t=0)}{\mathrm{LC}}$$

Region-based analysis. Statistics was mainly performed using the streamlines of SPM12 software package. First, the CMRg parametric images were created for each patient and spatially normalized in MNI space. To obtain adequate normalization, all [^{18}F]FDG PET image frames for each subject were re-aligned using the SPM12 software package (Wellcome Department of Cognitive Neurology, Institute of Neurology, London, UK, http://www.fil.ion.ucl.ac.uk/spm/) implemented in MATLAB 2015a. A mean PET image across all frames was created and was spatially normalized to the PET template in NMI space using FLIRT, part of FSL [35]. The resulted transformation matrix was then used to move CMRg parametric images to the MNI space. A quality control assessment was carried out after each normalization procedure. Smoothing with an isotropic Gaussian kernel of 8 mm FWHM (full-width at half-maximum) was then applied for all CMRg images.

Multiple volumes of interest (VOI) were automatically created and binarized based on the Harvard-Oxford cortical and subcortical structural atlases, part of FSL. Subsequently, region-based analysis was conducted to extract regional CMRg from different brain regions using fslmeants, part of FSL.

Measures of insulin sensitivity. Insulin sensitivity index was computed by ISIcomp according to the formula: 10.000/sqrt [fasting plasma glucose (mg/dl) × fasting plasma insulin (μUI/ml) × glucose at 120 min (mg/dl) × insulin at 120 min (μUI/ml)]. HOMA-IR was calculated according to the formula: fasting insulin (μUI/ml) × fasting glucose (mg/dl)/405. The oral disposition index (DI) was calculated as ISSI-2 equal to ISIcomp × AUCins/AUCgluc [36].

Area under the curve. The area under the curve (AUC) of metabolic parameters was calculated using the trapezoidal rule and incremental AUC (iAUC) with subtracted basal values.

Statistical analysis

For power calculation, in the absence of strong preliminary data on this specific clinical setting we have used data from a previous study [37] where the cerebral glucose metabolic rate during OGTT increased by 50% or more in several brain aeras with a mean difference around of 0.05 ± 0.01 μmol/(ml min) (mean ± SD) after subcutaneous injection of a GLP-1 agonist (exenatide). We have previously hypothesized that the effect of bariatric surgery on several aspects of brain function could be mediated by the well-known increase in GLP-1 [4]. Therefore, that difference and related SD was used for the power calculation showing that 8 subjects with obesity were needed to show statistical significance at alpha <0.05 with 95% power.

Data are expressed as mean ± SD or SE or as median (and range), as appropriate. Variables that were not normally distributed were log-transformed before analysis. Comparison between study variables was performed using parametric or non-parametric tests (e.g., paired *t* test or Wilcoxon test) for variables normally or non-normally distributed, respectively. Treatment-induced changes were examined by Wilcoxon's signed-rank test and a $p < 0.05$ (two-tailed analysis) was considered statistically significant. Correlations were assessed by using the Pearson's correlation coefficient (*r*) and statistical significance determined by a permutation test and *p* values were corrected for multiple comparisons using the Bonferroni method. To assess robustness of correlations, we also computed the Bayes Factor (BF). A BF < 0.3 was considered favouring the null hypothesis (no correlation), whereas a BF > 3 indicates supported the alternative hypothesis, i.e., robust correlation between the two variables of interest. All statistical analyses were performed using SPSS-2.0 (Statistical Package for Social Sciences, Chicago, IL, USA) and MATLAB software.

RESULTS

Subjects and effects of bariatric surgery on insulin sensitivity and metabolic parameters

Thirteen out of 20 subjects who underwent baseline evaluation completed the study. Three patients withdrew the consent to repeat post RYGB assessment and 4 were lost to follow-up. The main clinical and biochemical characteristics of all study participants before and after RYGB are summarized in Table 1. No subject experienced intraoperatively and/or post-operatively complications. Six months after bariatric surgery, BMI was reduced from 46.1 ± 4.9 kg/m^2 to 35.3 ± 5.0 kg/m^2 ($p < 0.01$). Fasting plasma glucose (FPG) concentrations slightly decreased, while HbA1c and lipid profile levels significantly improved (Table 1). After RYGB, plasma glucose and insulin levels during OGTT showed an earlier peak but lower 2-h concentration compared to baseline (data not shown). Both total (AUC) and incremental area under the curve (iAUC) of plasma glucose, insulin, and C-peptide were increased (Table 2). ISIcomp (from 2.4 ± 0.5 to 8.2 ± 1.9; $p = 0.004$) and the Disposition Index (from 1.1 ± 0.2 to 2.9 ± 1.1 ISSI-2; $p = 0.02$) improved in a significant manner (Table 2) along with a significant decrease in HOMA-IR (from 4.5 ± 2.4 to 1.6 ± 0.9; $p < 0.001$. Table 2). GLP-1 AUC and GLP-1 iAUC were significantly greater after surgery (Table 2), whereas GIP levels were different only at baseline (from

Table 1. Anthropometric and laboratory characteristics of study participants ($n = 13$) before and after Roux-en-Y gastric bypass (RYGB).

	Before RYGB	After RYGB	*p*
BMI (kg/m^2)	46.1 ± 4.9	35.3 ± 5.0	<0.01
SBP (mmHg)	129.0 ± 12.0	114.0 ± 5.0	0.19
DBP (mmHg)	85.0 ± 9.0	75.0 ± 5.0	0.30
FPG (mmol/l)	5.61 ± 0.72	5.22 ± 0.39	0.08
HbA1c (mmol/mol)	41.0 ± 6.0	38.0 ± 4.0	0.01
Total cholesterol (mmol/l)	4.97 ± 0.83	4.30 ± 0.54	0.001
HDL cholesterol (mmol/lL)	1.24 ± 0.23	1.39 ± 0.36	0.02
LDL cholesterol (mmol/l)	3.26 ± 0.80	2.48 ± 0.41	0.001
Triglycerides (mmol/l)	1.25 ± 0.54	0.91 ± 0.33	0.002

Data are expressed as mean ± SD.
BMI body mass index, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *FPG* fasting plasma glucose.

Table 2. Metabolic parameters and beta-cell function before and after Roux-en-Y gastric bypass (RYGB).

	Before RYGB	After RYGB	*p*
AUC glucose (mmol/l)	18.977 ± 3.494	21.660 ± 2.801	0.01
iAUC glucose (mmol/l)	6.949 ± 2.802	10.351 ± 2.399	0.001
AUC insulin (μUI/ml)	10.287 ± 7.017	11.927 ± 7.731	<0.02
iAUC insulin (μUI/ml)	8.124 ± 7.036	11.159 ± 7.730	0.03
AUC C-peptide (ng/ml)	947 ± 286	1.145 ± 403	<0.001
iAUC C-peptide (ng/ml)	518 ± 228	931 ± 370	<0.001
AUC total GLP-1 (ng/ml)	5.652 ± 1.806	10.441 ± 3.096	0.0008
iAUC total GLP-1 (ng/ml)	191 ± 370	6.581 ± 3.668	<0.001
AUC active GLP-1 (ng/ml)	3.020 ± 1.038	6.529 ± 2.731	0.003
iAUC active GLP-1 (ng/ml)	357 ± 356	4.345 ± 3.449	0.001
Matsuda Index (ISIcomp)	2.4 ± 0.5	8.2 ± 1.9	0.004
HOMA-IR	4.5 ± 2.4	1.6 ± 0.9	<0.001
Disposition Index	1.1 ± 0.2	2.9 ± 1.1	0.02
GIP (pg/l)	25.6 ± 6.9	30.5 ± 8.1	0.02
Leptin (ng/dl)	80.4 ± 13.0	16.1 ± 2.4	0.001
BDNF (ng/ml)	196.9 ± 24.5	214.5 ± 52	0.67

Data are expressed as median and range or mean ± SD.
AUC total area under the curve, *iAUC* incremental area under the curve, *BDNF* brain-derived neurotrophic factor.

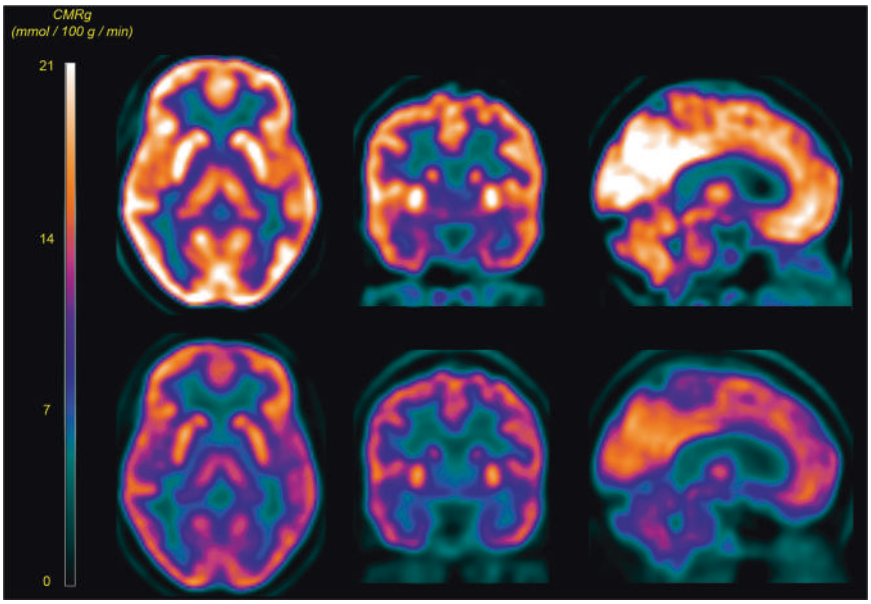

Fig. 1 Cerebral metabolic rate of glucose in a patient before (upper panel) and after (lower panel) Roux-en-Y Gastric Bypass. PET images are spatially co-registered and scaled according to absolute values of cerebral metabolic rate of glucose.

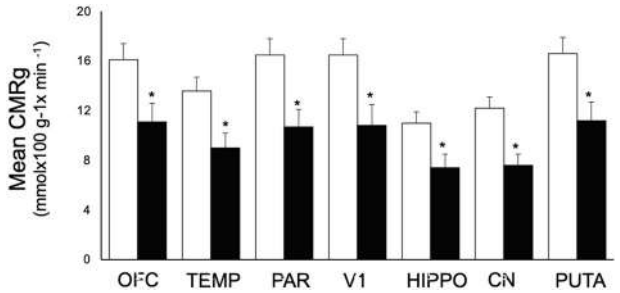

Fig. 2 Glucose metabolic rate in brain regions before (white bars) and after (dark bars) Roux-en-Y Gastric Bypass. CMRg glucose metabolic rate, OFC orbitofrontal cortex, TEMP temporal lobe; PAR parietal lobe, V1 primary visual cortex, HIPPO hippocampus, CN caudate nucleus, PUTA putamen. Error bars represent the SEM; *all $p = 0.01$ or less (Wilcoxon signed-rank test).

Table 3. Scores for each cognitive test before and after Roux-en-Y gastric bypass (RYGB).

	Before RYGB	After RYGB	p
MMSE	28 (25–30)	30 (28–30)	0.001
MoCA	25 (19–30)	28 (24–30)	0.002
Visuospatial skills	3.6 ± 0.8	4.4 ± 0.6	0.04
Abstraction	1.3 ± 0.8	1.8 ± 0.3	<0.05
TMT-A	46.3 ± 26.5	37.0 ± 12.7	0.07
TMT-B	92.7 ± 47.0	85.6 ± 39.6	0.08
Token test	31.3 ± 3.5	32.6 ± 1.9	0.19
PHQ-9	2.58 ± 1.6	1.67 ± 0.98	0.11

Data are expressed as median and range or mean ± SE.
MMSE Mini Mental State Examination, *MoCA* Montreal Cognitive Assessment, *TMT-A* Trail Making test part A, *TMT-B* Trail Making test part B, *PHQ-9* Patient Health Questionnaire-9.

25.6 ± 6.9 pg/L to 30.5 ± 8.1 pg/L; $p = 0.02$) (Table 2) with no significant differences during OGTT. No change was apparent in VIP (data not shown) or BDNF, while fasting plasma leptin concentrations were significantly lower after RYGB (Table 2).

Effect of bariatric surgery on brain glucose metabolism

At baseline, CMRg was homogeneous and symmetrical with no areas of higher or lower activity. Six months after RYGB, CMRg was markedly diminished (Fig. 1) in several brain regions of interest (i.e., orbitofrontal cortex, temporal lobe, parietal lobe, primary visual cortex, hippocampus, caudate and putamen nucleus; all $p = 0.01$ or less; Fig. 2).

Effect of bariatric surgery on cognitive performance

Table 3 summarizes the results of the cognitive function tests. The MMSE score at baseline fell within the normal values (median 28; range 25–30), with no evidence of cognitive impairments, whereas the MoCA score (median 25, range 19–30) fell below the optimal cut-off value of 26, suggesting a mild global cognitive dysfunction. A low performance was more apparent for visuospatial abilities, executive functioning, and abstraction. Results from TMT and TT excluded significant disorders of executive function and receptive language, respectively. The average PHQ-9 score at baseline was 2.58 ± 1.6, excluding the presence of depression symptoms.

Six months after RYGB, an increase was detected for both MMSE [from 28 (25–30) to 30 (range 28–30), $p = 0.001$] and MoCA score [from 25 (19–30) to 28 (range 24–30), $p = 0.002$] with the largest improvement occurring in visuospatial/executive skills and in the domain of abstraction (from 3.6 ± 0.8 to 4.4 ± 0.6, $p = 0.04$ and from 1.3 ± 0.8 to 1.8 ± 0.3, $p < 0.05$, respectively). At follow-up, the time for completion of the TMT-A improved slightly (from 46.3 ± 26.5 to 37.0 ± 12.7 s), approaching the statistical significance ($p = 0.07$). Similarly, the time for completion of the TMT-B was shorter following surgery (from 92.7 ± 47 to 85.6 ± 39.6 s) ($p = 0.08$), thus reflecting a better performance. The variation between the total Token Test scores in the two sessions was not significant. Similarly, no clinically significant changes were observed in the PHQ-9 score at follow-up (1.67 ± 0.98; $p = 0.11$ vs baseline).

Exploratory correlational analyses

In the attempt to determine whether any of the variable affected by RYGB could account for CMRg changes (CMRg after RYGB - CMRg baseline), we performed exploratory correlation analyses.

HOMA-IR changes were associated with CMRg changes in the caudate nucleus ($\rho = 0.65$, $p = 0.01$). CMRg changes in the hippocampus were also correlated with changes in plasma leptin ($\rho = 0.50$; $p = 0.008$). No correlation was found between CMRg changes and BMI or gut hormones and BDNF level.

Then we sought for correlations between cerebral glucose metabolism and cognitive scores. TMT-A changes were correlated with CMRg changes in the parietal lobe ($\rho = -0.60$, $p = 0.03$), putamen ($\rho = -0.58$, $p = 0.04$) and visual cortex ($\rho = -0.60$, $p = 0.04$). A similar numerical trend was observed in the temporal lobe, hippocampus, and orbitofrontal cortex. Moreover, Token test changes correlated with CMRg changes in the orbitofrontal cortex ($\rho = 0.64$, $p = 0.03$), parietal lobe ($\rho = 0.69$, $p = 0.01$), temporal lobe ($\rho = 0.68$, $p = 0.02$), hippocampus ($\rho = 0.66$, $p = 0.02$), putamen ($\rho = 0.66$, $p = 0.02$), and primary visual cortex ($\rho = 0.60$, $p = 0.04$). In a stepwise analysis, CMRg in the temporal lobe emerged as the strongest predictor of changes in Token test and TMT-A (F value 8.9, $p = 0.01$ and F value 5.7, $p = 0.04$, respectively). No correlation was found between BMI, HbA1c, hormones or metabolites and any of the cognitive test.

DISCUSSION

The main findings of our study can be summarized as follows: (i) bariatric surgery (RYGB) is associated with attenuation of cerebral glucose metabolic rate (CMRg); (ii) the changes in CMRg are directly related with the improvement of cognitive performance; (iii) changes in cerebral glucose utilization following surgery are associated with improved insulin resistance and plasma leptin reduction.

As compared to lean subjects, higher cerebral metabolic rates have been reported in insulin-resistant individuals with obesity [10], and in subjects with type 2 diabetes [11]. Perturbed cerebral glucose metabolism has been also reported in young subjects with high risk for future obesity [12]. In line with recent evidence [14, 20, 38], we found a marked attenuation of brain glucose uptake after bariatric surgery. In our study, we have also shown that these changes are directly related to improvement of cognitive performance. Although it is suggested that excess adiposity is a risk factor for reduced cognitive scores [39], in our study, at baseline, there was no evidence of manifest cognitive impairment, yet subtle deficits were apparent on MoCA, especially with respect to visuospatial/ executive skills, and abstraction. As already described by others [17–20, 23, 40], cognitive performance improved significantly following surgery with the largest improvement occurred in visuospatial/executive skills as compared to baseline performance. These associations, yet not being a proof of a cause-effect relationship, might point to brain efficiency model of cognitive performance although other mechanisms may be in place. In subjects with obesity or glucose intolerance [10, 14] elevation of brain glucose uptake is associated with greater endogenous glucose production and lower peripheral glucose utilization reflecting a condition of insulin resistance at the level of each one of these organs [41]. In keeping with this interpretation, peripheral insulin resistance has been found to be directly related to brain insulin resistance, either due to reduced insulin transport or changes in insulin receptor sensitivity and activation [42]. Under these circumstances, the presence of increased metabolic activity in brain regions could be interpreted as a functional compensation in the face of impaired insulin signalling. Insulin plays a critical role in brain health [43], and significant disturbances in brain insulin action have been observed in obesity and type 2 diabetes as well as in aging and dementia [44]. Of interest, we found that surgery-mediated improvement of insulin resistance was correlated with CMRg changes, in keeping with the hypothesis that impaired insulin action on the central nervous may provide a link between metabolic and brain dysfunctions. The correlation between HOMA-IR changes and CMRg changes was significant in the caudate nucleus, a brain region, in individuals affected by obesity, with low regional brain volume [45] and higher glucose uptake [46]. In our study, we found that the change in CMRg at the level of the temporal lobe appears to drive the correlation with the change in some cognitive abilities. Recent evidence suggests that altered connectivity within the temporal system is associated with early changes in preclinical Alzheimer's disease [47]. Therefore, we speculate that the temporal lobe, by virtue of its rich connections, could play a pivotal role in brain changes.

Our findings are in keeping with previous studies demonstrating partial reversibility of impaired insulin-stimulated hypothalamic response [48] after massive reduction of body weight in people with obesity [49].

The possibility that the attenuation of brain glucose uptake and improved cognitive performance may be mediated by mechanisms other than changes in insulin sensitivity should be considered as well. For instance, the release of GLP-1, an incretin known to affect brain function [50–52], is increased after RYGB. However, no association was found between changes in GLP-1 as well as GIP and VIP, nor it was an association with BDNF, a marker of neuronal number and viability, CMRg or cognitive performance. Conversely, our data point to a potential brain–adipose tissue crosstalk as indicated by the correlation existing between CMRg changes after bariatric surgery in the hippocampus, a site implicated in cognitive processes, and reduction in plasma leptin concentration as also previously reported by Alosco et al [27]. Whether this is the consequence of increased the brain's sensitivity to leptin (i.e., decreased leptin resistance) or simply reflect body energy status remains to be sorted out. Similarly, what remains to be ascertained is whether the increase in CMRg represents a compensatory response to early neuronal damage [53] or a maladaptive overactivity ("running hot") of internal cortical circuitry [54] or an expression of the insulin/leptin resistance, as suggested from our data. This association with leptin changes is in line with our previous observation or a relationship between changes in leptin and visual brain plasticity in people with obesity undergoing RYGB [4]. To which extent, changes in CMRg may be related to improvements in visual neuronal plasticity was not assessed in the present study. However, the signifying attenuation of CMRg in many brain areas, including the visual cortex, support the hypothesis that improvement of brain insulin sensitivity may at least contribute to visual brain plasticity.

From a neuropsychiatric perspective, obesity displays complex associations with mood and eating disorders, attention deficit and executive dysfunctions [55], which, to some extent, may be related to the cognitive performance. However, the size of our study population is not sufficient to explore in a reliable manner a relationship between cognition and psychologic changes and this goes beyond the primary objective of the study.

Much of our results is based on changes in cognitive performance after bariatric surgery. A critical point in exploring cognitive function during the repeated testing is the "practice effect", namely the expected improvement in cognitive test performance due to repeated evaluation with the same test materials [56], that may complicate result interpretation. However, we believe that practice effect in our study may be reasonably excluded. Indeed, practice effects seem to be clinically relevant during high frequency testing up to month 3, while 'no effect' is observed from month 3 to 6 or 12 [57]. On the other hand, an attenuation of practice effects on neuropsychological performance is a potential marker of preclinical Alzheimer's disease [58]. Finally, the time interval between baseline and follow-up in our study (6 months) is similar or longer as compared to other studies that evaluate the effects of bariatric surgery on cognitive function [20, 25, 40, 59, 60]

There are limitations to the present study that should be taken into consideration. First, the sample size was small, and that was

partially justified by the complexity of the study design. However, since ours is a hypothesis-generating pilot study, relative value of the results remains valid. The presence of a control group (i.e., patients not candidates to bariatric surgery) could have strengthened the study, although our approach is in line with other recent studies [25]. Similarly, one could argue a control group including people undergoing different weight reduction procedure could have been of interest. However, comparison among different techniques goes beyond the scope of the present study. Moreover, recent reports have shown that the type of surgical procedure does not differentially affect cognitive performance [59]. The correlations between changes of brain metabolism and insulin and leptin sensitivity after surgery do not imply causality, yet they are hypothesis generating allowing a more focused design of future studies to unravel the complexity of the brain-adipocyte network.

While accepting these weaknesses, we would like to underline some potential strengths of our study. To the best of our knowledge, this is the first study evaluating obesity-brain function relationship by [^{18}F]FDG PET during an oral glucose load with the potential for factoring in the activation of the incretin axis, which is not possible to do with euglycemic insulin clamp condition as done in the past. Also, the combination of neuroimaging and neurocognitive tests is a feature of our study. We chose a battery of standardized neurocognitive tests exploring several cognitive domains and as such providing a good overview of overall cognitive performance. These tests do not require much time to be completed avoiding subjective fatigue.

In conclusion, we have shown that bariatric surgery is associated with reduced brain glucose utilization and such reduction correlates with improvements in cognitive performance. Were these findings supported by larger-scale studies, they would provide strong evidence for an amelioration of brain function and cognitive performance of adult individuals to be mediated by prevention or treatment of overweight and obesity. The mechanisms underlying the "brain effect" of bariatric surgery remain to be elucidated, although the restoration of insulin and leptin sensitivity may have a role, which could be potentially targeted also with pharmacologic interventions. Neuroimaging, neurocognitive tests, multiple metabolic parameters combined each together in future longitudinal, observational studies with longer follow-up may add important pieces in brain-obesity puzzle.

DATA AVAILABILITY

Data are available on request from AD and GD.

REFERENCES

1. O'Brien PD, Hinder LM, Callaghan BC, Feldman EL. Neurological consequences of obesity. Lancet Neurol. 2017;16:465–77.
2. Baskaran C, Animashaun A, Rickard F, Toth AT, Eddy KT, Plessow F, et al. Memory and executive function in adolescent and young adult females with moderate to severe obesity before and after weight loss surgery. Obes Surg. 2021;31:3372–8.
3. Lunghi C, Daniele G, Binda P, Dardano A, Ceccarini G, Santini F, et al. Altered visual plasticity in morbidly obese subjects. iScience. 2019;22:206–13.
4. Daniele G, Lunghi C, Dardano A, Binda P, Ceccarini G, Santini F, et al. Bariatric surgery restores visual cortical plasticity in nondiabetic subjects with obesity. Int J Obes. 2021;45:1821–9.
5. Miller AA, Spencer SJ. Obesity and neuroinflammation: a pathway to cognitive impairment. Brain Behav Immun. 2014;42:10–21.
6. Forny-Germano L, De Felice FG, Vieira MNDN. The role of leptin and adiponectin in obesity-associated cognitive decline and Alzheimer's disease. Front Neurosci. 2019;12:1027.
7. Ekblad LL, Rinne JO, Puukka P, Laine H, Ahtiluoto S, Sulkava R, et al. Insulin resistance predicts cognitive decline: an 11-year follow-up of a nationally representative adult population sample. Diabetes Care. 2017;40:751–8.
8. Carnell S, Gibson C, Benson L, Ochner CN, Geliebter A. Neuroimaging and obesity: current knowledge and future directions. Obes Rev. 2012;13:43–56.
9. Iozzo P, Guzzardi MA. Imaging of brain glucose uptake by PET in obesity and cognitive dysfunction: life-course perspective. Endocr Connect. 2019;8:R169–83.
10. Hirvonen J, Virtanen KA, Nummenmaa L, Hannukainen JC, Honka MJ, Bucci M, et al. Effects of insulin on brain glucose metabolism in impaired glucose tolerance. Diabetes. 2011;60:443–7.
11. Rebelos E, Bucci M, Karjalainen T, Oikonen V, Bertoldo A, Hannukainen JC, et al. Insulin resistance is associated with enhanced brain glucose uptake during euglycemic hyperinsulinemia: a large-scale PET cohort. Diabetes Care. 2021;44:788–94.
12. Kantonen T, Pekkarinen L, Karjalainen T, Bucci M, Kalliokoski K, Haaparanta-Solin M, et al. Obesity risk is associated with altered cerebral glucose metabolism and decreased μ-opioid and CB1 receptor availability. Int J Obes. 2022;46:400–7.
13. Pareek M, Schauer PR, Kaplan LM, Leiter LA, Rubino F, Bhatt DL. Metabolic surgery: weight loss, diabetes, and beyond. J Am Coll Cardiol. 2018;71:670–87.
14. Tuulari JJ, Karlsson HK, Hirvonen J, Hannukainen JC, Bucci M, Helmiö M, et al. Weight loss after bariatric surgery reverses insulin-induced increases in brain glucose metabolism of the morbidly obese. Diabetes. 2013;62:2747–51.
15. Tuulari JJ, Karlsson HK, Antikainen O, Hirvonen J, Pham T, Salminen P, et al. Bariatric surgery induces white and grey matter density recovery in the morbidly obese: a voxel-based morphometric study. Hum Brain Mapp. 2016;37:3745–56.
16. Zhang Y, Ji G, Xu M, Cai W, Zhu Q, Qian L, et al. Recovery of brain structural abnormalities in morbidly obese patients after bariatric surgery. Int J Obes. 2016;40:1558–65.
17. Miller LA, Crosby RD, Galioto R, Strain G, Devlin MJ, Wing R, et al. Bariatric surgery patients exhibit improved memory function 12 months postoperatively. Obes Surg. 2013;23:1527–35.
18. Alosco ML, Spitznagel MB, Strain G, Devlin M, Cohen R, Paul R, et al. Improved memory function two years after bariatric surgery. Obesity. 2014;22:32–38.
19. Alosco ML, Galioto R, Spitznagel MB, Strain G, Devlin M, Cohen R, et al. Cognitive function after bariatric surgery: evidence for improvement 3 years after surgery. Am J Surg. 2014;207:870–6.
20. Marques EL, Halpern A, Corrêa Mancini M, de Melo ME, Horie NC, Buchpiguel CA, et al. Changes in neuropsychological tests and brain metabolism after bariatric surgery. J Clin Endocrinol Metab. 2014;99:E2347–52.
21. Spitznagel MB, Hawkins M, Alosco M, Galioto R, Garcia S, Miller L, et al. Neurocognitive effects of obesity and bariatric surgery. J. Eur Eat Disord Rev. 2015;23:488–95.
22. Handley JD, Williams DM, Caplin S, Stephens JW, Barry J. Changes in cognitive function following bariatric surgery: a systematic review. Obes Surg. 2016;26:2530–7.
23. Rochette AD, Spitznagel MB, Strain G, Devlin M, Crosby RD, Mitchell JE, et al. Mild cognitive impairment is prevalent in persons with severe obesity. Obesity. 2016;24:1427–9.
24. Nota MHC, Vreeken D, Wiesmann M, Aarts EO, Hazebroek EJ, Kiliaan AJ. Obesity affects brain structure and function-rescue by bariatric surgery? Neurosci Biobehav Rev. 2020;108:646–57.
25. Saindane AM, Drane DL, Singh A, Wu J, Qiu D. Neuroimaging correlates of cognitive changes after bariatric surgery. Surg Obes Relat Dis. 2020;16:119–27.
26. Mejido DCP, Peny JA, Vieira MNN, Ferreira ST, De, Felice FG. Insulin and leptin as potential cognitive enhancers in metabolic disorders and Alzheimer's disease. Neuropharmacology. 2020;171:108115.
27. Alosco ML, Spitznagel MB, Strain G, Devlin M, Cohen R, Crosby RD, et al. Improved serum leptin and ghrelin following bariatric surgery predict better postoperative cognitive function. Clin Neurol. 2015;11:48–56.
28. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res. 1975;12:189–98.
29. Nasreddine ZS, Phillips NA, Bédirian V, Charbonneau S, Whitehead V, Collin I, et al. The Montreal Cognitive. Assessment, MoCA: a brief screening tool for mild cognitive impairment. Am Geriatr Soc. 2005;53:695–9.
30. Bowie CR, Harvey PD. Administration and interpretation of the Trail Making Test. Nat Protoc. 2006;1:2277–81.
31. De Renzi E, Vignolo LA. The token test: a sensitive test to detect receptive disturbances in aphasics. Brain. 1962;85:665–78.
32. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. J Gen International Med. 2001;16:606–13.
33. Chen K, Bandy D, Reiman E, Huang SC, Lawson M, Feng D, et al. Noninvasive quantification of the cerebral metabolic rate for glucose using positron emission tomography, 18F-fluoro-2-deoxyglucose, the Patlak method, and an image-derived input function. Cereb Blood Flow Metab. 1998;18:716–23.
34. Dunn JT, Anthony K, Amiel SA, Marsden PK. Correction for the effect of rising plasma glucose levels on quantification of MR(glc) with FDG-PET. J Cereb Blood Flow Metab. 2009;29:1059–67.

35. Smith SM, Jenkinson M, Woolrich MW, Beckmann CF, Behrens TE, Johansen-Berg H, et al. Advances in functional and structural MR image analysis and implementation as FSL. Neuroimage. 2004;23:S208–19.
36. Retnakaran R, Qi Y, Goran MI, Hamilton JK. Evaluation of proposed oral disposition index measures in relation to the actual disposition index. Diabet Med. 2009;26:1198–s203.
37. Daniele G, Iozzo P, Molina-Carrion M, Lancaster J, Ciociaro D, Cersosimo E, et al. Exenatide regulates cerebral glucose metabolism in brain areas associated with glucose homeostasis and reward system. Diabetes. 2015;64:3406–12.
38. Almby KE, Lundqvist MH, Abrahamsson N, Kvernby S, Fahlström M, Pereira MJ, et al. Effects of gastric bypass surgery on the brain: simultaneous assessment of glucose uptake, blood flow, neural activity, and cognitive function during normo- and hypoglycemia. Diabetes. 2021;70:1265–77.
39. Anand SS, Friedrich MG, Lee DS, Awadalla P, Després JP, Desai D, et al. Evaluation of adiposity and cognitive function in adults. JAMA Netw Open. 2022;5:e2146324.
40. Smith KR, Moran TH, Papantoni A, Speck C, Bakker A, Kamath V, et al. Short-term improvements in cognitive function following vertical sleeve gastrectomy and Roux-en Y gastric bypass: a direct comparison study. Surg Endosc. 2020;34:2248–57.
41. Rebelos E, Immonen H, Bucci M, Hannukainen JC, Nummenmaa L, Honka MJ, et al. Brain glucose uptake is associated with endogenous glucose production in obese patients before and after bariatric surgery and predicts metabolic outcome at followup. Diabetes Obes Metab. 2019;21:218–26.
42. Kellar D, Craft S. Brain insulin resistance in Alzheimer's disease and related disorders: mechanisms and therapeutic approaches. Lancet Neurol. 2020;19:758–66.
43. Taouis M, Torres-Aleman I. Editorial: insulin and the brain. Front Endocrinol. 2019;10:299.
44. Kullmann S, Heni M, Hallschmid M, Fritsche A, Preissl H, Häring HU. Brain insulin resistance at the crossroads of metabolic and cognitive disorders in humans. Physiol Rev. 2016;96:1169–209.
45. Hamer M, Batty GD. Association of body mass index and waist-to-hip ratio with brain structure: UK Biobank study. Neurology. 2019;92:e594–e600.
46. Nummenmaa L, Hirvonen J, Hannukainen JC, Immonen H, Lindroos MM, Salminen P, et al. Dorsal striatum and its limbic connectivity mediate abnormal anticipatory reward processing in obesity. PLoS ONE. 2012;7:e31089.
47. Berron D, van Westen D, Ossenkoppele R, Strandberg O, Hansson O. Medial temporal lobe connectivity and its associations with cognition in early Alzheimer's disease. Brain. 2020;143:1233–48.
48. Matsuda M, Liu Y, Mahankali S, Pu Y, Mahankali A, Wang J, et al. Altered hypothalamic function in response to glucose ingestion in obese humans. Diabetes. 1999;48:1801–6.
49. van de Sande-Lee S, Pereira FR, Cintra DE, Fernandes PT, Cardoso AR, Garlipp CR, et al. Partial reversibility of hypothalamic dysfunction and changes in brain activity after body mass reduction in obese subjects. Diabetes. 2011;60:1699–704.
50. Long-Smith CM, Manning S, McClean PL, Coakley MF, O'Halloran DJ, Holscher C, et al. The diabetes drug liraglutide ameliorates aberrant insulin receptor localisation and signalling in parallel with decreasing both amyloid-β plaque and glial pathology in a mouse model of Alzheimer's disease. Neuromolecular Med. 2013;15:102–14.
51. Gejl M, Gjedde A, Egefjord L, Møller A, Hansen SB, Vang K, et al. In Alzheimer's disease, 6-month treatment with GLP-1 analog prevents decline of brain glucose metabolism: randomized, placebo-controlled, double-blind clinical trial. Front Aging Neurosci. 2016;8:108.
52. Binda P, Eldor R, Huerta C, Adams J, Lancaster J, Fox P, et al. Exenatide modulates visual cortex responses. Diabetes Metab Res Rev. 2019;35:e3167.
53. Ashraf A, Fan Z, Brooks DJ, Edison P. Cortical hypermetabolism in MCI subjects: a compensatory mechanism? Eur J Nucl Med Mol Imaging. 2015;42:447–58.
54. Apostolova I, Lange C, Mäurer A, Suppa P, Spies L, Grothe MJ, et al. Hypermetabolism in the hippocampal formation of cognitively impaired patients indicates detrimental maladaptation. Neurobiol Aging. 2018;65:41–50.
55. Weiss F, Barbuti M, Carignani G, Calderone A, Santini F, Maremmani I, et al. Psychiatric aspects of obesity: a narrative review of pathophysiology and psychopathology. J Clin Med. 2020;9:2344.
56. Salthouse TA. Robust cognitive change. J Int Neuropsychol Soc. 2012;18:749–56.
57. Bartels C, Wegrzyn M, Wiedl A, Ackermann V, Ehrenreich H. Practice effects in healthy adults: a longitudinal study on frequent repetitive cognitive testing. BMC Neurosci. 2010;11:118.
58. Hassenstab J, Ruvolo D, Jasielec M, Xiong C, Grant E, Morris JC. Absence of practice effects in preclinical Alzheimer's disease. Neuropsychology. 2015;29:940–8.
59. Prehn K, Profitlich T, Rangus I, Heßler S, Witte AV, Grittner U, et al. Bariatric surgery and brain health-a longitudinal observational study investigating the effect of surgery on cognitive function and gray matter volume. Nutrients. 2020;12:127.
60. Tucker WJ, Thomas BP, Puzziferri N, Samuel TJ, Zaha VG, Lingvay I, et al. Impact of bariatric surgery on cerebral vascular reactivity and cognitive function: a non-randomized pilot study. Pilot Feasibility Stud. 2020;6:21.

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AUTHOR CONTRIBUTIONS

AD, GD, and SDP contributed to the conception and design of the experiments and were responsible for data collection, analysis, and interpretation; AD, GD, AC, GC, and FS recruited the subjects; GD and AD performed clinical examinations; AD also performed neurocognitive examinations; VSB performed lab measurements; CM and RB performed surgery; GA and DV performed PET studies and analysis; GD performed statistical analysis; AD wrote the first version of the paper; AD, SDP, and GD discussed the results and wrote the final version of the paper. All authors approved the final version of the manuscript for submission. AD and GD are guarantors of this work, who have full access to all the data in this study and take responsibility for the integrity and accuracy of the data.

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COMPETING INTERESTS

The authors declare no competing interests.

ETHICS STATEMENT

Written informed consent was obtained from all subjects.

ADDITIONAL INFORMATION

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Correspondence and requests for materials should be addressed to Stefano Del Prato.

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