Received: 22 January 2020 | Revised: 5 February 2020 | Accepted: 9 February 2020

DOI: 10.1111/dom.13996

ORIGINAL ARTICLE

WILEY

Brain free fatty acid uptake is elevated in morbid obesity, and is irreversible 6 months after bariatric surgery: A positron emission tomography study

Eleni Rebelos MD[1,2] | Jussi Hirvonen MD[3] | Marco Bucci PhD[1,2] | Laura Pekkarinen MD[1] | Mikko Nyman MD[3] | Jarna C. Hannukainen PhD[1] | Patricia Iozzo MD[1,4] | Paulina Salminen MD[5] | Lauri Nummenmaa PhD[1,6] | Ele Ferrannini MD[4] | Pirjo Nuutila MD[1,7]

[1]Turku PET Centre, University of Turku, Turku, Finland

[2]Turku PET Centre, Åbo Akademi, Turku, Finland

[3]Department of Radiology, Turku University Hospital and University of Turku, Turku, Finland

[4]Institute of Clinical Physiology, National Research Council (CNR), Pisa, Italy

[5]Department of Digestive Surgery and Urology, Turku University Hospital, Turku, Finland

[6]Department of Psychology, University of Turku, Turku, Finland

[7]Department of Endocrinology, Turku University Hospital, Turku, Finland

Correspondence
Pirjo Nuutila, Turku PET Centre, University of Turku, and Department of Endocrinology, Turku University Hospital, Turku, Finland.
Email: pirjo.nuutila@utu.fi

Funding information
The study was conducted within the Center of Excellence in Cardiovascular and Metabolic Diseases, supported by the Academy of Finland (grant 307402), the University of Turku, Turku University Hospital, Åbo Akademi University, Finnish Diabetes Foundation, and Sigrid Juselius Foundation; Åbo Akademi; Turku University Hospital; University of Turku; Academy of Finland; Åbo Akademi; Turku University Hospital; University of Turku; Academy of Finland

Peer Review
The peer review history for this article is available at https://publons.com/publon/10.1111/dom.13996.

Abstract

Aim: To investigate whether there are differences in brain fatty acid uptake (BFAU) between morbidly obese and lean subjects, and the effect of weight loss following bariatric surgery.

Materials and methods: We measured BFAU with 14(*R*, S)-[^{18}F]fluoro-6-thia-heptadecanoic acid and positron emission tomography in 24 morbidly obese and 14 lean women. Obese subjects were restudied 6 months after bariatric surgery. We also assessed whether there was hypothalamic neuroinflammation in the obese subjects using fluid-attenuated inversion recovery (FLAIR) magnetic resonance imaging.

Results: Obese subjects had a higher BFAU than lean subjects (1.12 [0.61] vs. 0.72 [0.50] μmol 100 g^{-1} min^{-1}, $P = 0.0002$), driven by higher fatty acid uptake availability. BFAU correlated positively with BMI ($P = 0.006$, $r = 0.48$), whole body fatty acid oxidation ($P = 0.006$, $r = 0.47$) and leptin levels ($P = 0.001$, $r = 0.54$). When BFAU, leptin and body mass index (BMI) were included in the same model, the association between BFAU and leptin was the strongest. BFAU did not correlate with FLAIR-derived estimates of hypothalamic inflammation. Six months after bariatric surgery, obese subjects achieved significant weight loss (−10 units of BMI). BFAU was not significantly changed (1.12 [0.61] vs. 1.09 [0.39] μmol 100 g^{-1} min^{-1}, ns), probably because of the ongoing catabolic state. Finally, baseline BFAU predicted worse plasma glucose levels at 2 years of follow-up.

Conclusions: BFAU is increased in morbidly obese compared with lean subjects, and is unchanged 6 months after bariatric surgery. Baseline BFAU predicts worse plasma

glucose levels at follow-up, supporting the notion that the brain participates in the control of whole-body homeostasis.

KEYWORDS
bariatric surgery, brain metabolism, free fatty acids, obesity, positron emission tomography

1 | INTRODUCTION

Obesity is a major public health burden as it is associated with an enhanced risk of cardiovascular disease, type 2 diabetes (T2D), stroke, neurodegenerative diseases and many types of cancer.[1,2] Obesity is linked with systemic low-grade inflammation.[3] Several lines of research in animals further show that a high-fat diet (HFD) leads to neuroinflammation and, particularly, astrocyte proliferation and activation (ie, astrogliosis). This process can occur even after only 1 day of HFD, and precede the establishment of systemic inflammation.[4]

For a long time, it was believed that the brain did not use free fatty acids (FFA). This notion has been challenged by preclinical and clinical studies. In the brain, astrocytes oxidize FFA[5] and oligodendrocytes have also been shown to take up FFA.[6] Astrocytes are able to deposit fatty acids into lipids, which are later released to the extracellular space and taken up by neurons.[7] Studies of brain FFA handling in humans are scarce. Almost 10 years ago, using positron emission tomography (PET) and two fatty acid analogues, we showed that brain fatty acid uptake (BFAU) was increased in subjects with metabolic syndrome compared with lean controls, and that BFAU decreased after weight loss.[8] Despite interest in the central effects of fatty acids, these findings have not been replicated.

In the current work, we sought to determine whether our previous findings on BFAU hold true in morbidly obese women compared with lean women. In addition, we examined the effects of bariatric surgery on BFAU. In particular, we hypothesized that morbidly obese women have higher BFAU than lean women, and that after major surgery-induced weight loss, BFAU is decreased. Because obese subjects often consume a HFD, we further hypothesized that neuroinflammation might also be present. Therefore, we measured the ratio of hypothalamic-to-amygdala signal intensity from fluid-attenuated inversion recovery (FLAIR) magnetic resonance imaging (MRI), which has been previously shown to reflect hypothalamic inflammation.[4,9,10] Finally, we analysed follow-up data to test whether baseline BFAU predicts any metabolic outcome after bariatric surgery, such as plasma glucose levels and HbA1c.

2 | MATERIALS AND METHODS

2.1 | Participants and study design

We studied 24 morbidly obese women and 14 age- and sex-matched healthy nonobese controls. Obese patients were studied before and 6 months after bariatric surgery; controls were studied only once. Inclusion and exclusion criteria and the surgical techniques have been previously described in detail.[11] Based on American Diabetes Association criteria,[12] nine obese patients had T2D and 15 were nondiabetic, including four with impaired glucose tolerance and one with impaired fasting glucose before the operation. Nine of the obese subjects had a diagnosis of arterial hypertension. Seven obese subjects underwent laparoscopic Roux-en-Y gastric bypass and 14 underwent laparoscopic sleeve gastrectomy (three subjects did not undergo surgery). The protocol was approved by the Ethics Committee of the Hospital District of Southwestern Finland, and all subjects gave written informed consent before participating in the study (NCT01373892).

2.2 | Study protocol

Clinical screening, anthropometric and biochemical measurements were performed as described.[13] Subjects then underwent PET/computerized tomography (CT) measurements in the fasting state using a hybrid General Electric discovery STE and VCT scanners (General Electric Medical Systems, Milwaukee, WI, USA). In obese patients, the imaging studies were performed before the standard 4-week very-low calorie diet that preceded surgery. Following an overnight (10–12 hour) fast, two catheters were inserted in the antecubital veins, one for the administration of radiolabelled tracers and the other for arterialized blood sampling. Then an intravenous bolus (185 ± 46 MBq) of the long-chain fatty acid analogue 14(*R*,*S*)-[^{18}F]fluoro-6-thia-heptadecanoic acid ([^{18}F]-FTHA) was given, following which the dynamic PET imaging of the brain started and continued for 40 minutes. Blood samples were drawn during the entire scanning period to measure FFA as well as radioactivity levels.

2.3 | Quantification of BFAU

The brain fractional uptake rate (FUR) of [^{18}F]-FTHA was calculated by dividing brain radioactivity by the integral of the plasma unmetabolized radioactivity curve.[14] BFAU (in μmol 100 g^{-1} min^{-1}) was then calculated at voxel level as the product of FUR and serum FFA concentration.[8]

2.4 | Indirect calorimetry

Open-system indirect calorimetry (Deltatrac) was used for the measurement of O_2 consumption (VO_2) and CO_2 production (VCO_2), from

which whole-body energy expenditure and substrate oxidation rates were calculated, as previously described.[15]

2.5 | Calculations

Insulin sensitivity was estimated by the oral glucose insulin sensitivity (OGIS) method and expressed in mL min^{-1} m^{-2}.[16]

2.6 | FLAIR-derived measurement and reliability

To measure mediobasal hypothalamic (MBH) gliosis, the signal intensity (SI) was retrospectively measured from coronally oriented FLAIR images from MRI, as previously described.[4,9,10] FLAIR images were gathered as part of the study protocol by a Philips 1.5 T device (Philips Ingenuity) with the following image variables: time of repetition 11000 ms, time of echo 140 ms, time of inversion 2800 ms, slice thickness 5 mm. Briefly, circular regions of interest (ROIs, ~ 4 mm^2) were placed on one coronal slice onto MBH, which was identified as a bilateral, most caudal brain region situated between the optic chiasm anteriorly and the mamillary bodies posteriorly. The amygdala, visible on the same slice in the medial temporal lobe, was chosen as the reference region (ROI of ~ 20 mm^2) for the normalization of MBH SI, and the MBH-amygdala SI ratio served as the primary outcome measure of hypothalamic gliosis. All measurements were carried out by a fellowship-trained neuroradiologist (J.H.). To assess reliability of measurement, 30 cases were independently analysed by another fellowship-trained neuroradiologist (M.N.), blind to the assessment by the other reader. We assessed interrater reliability by variability (absolute difference between measurements by two raters, divided by the average of those measurements), and intraclass correlation coefficients (ICC), where <0.5 is poor, 0.5–0.75 is moderate, 0.75–0.9 is good, and > 0.9 represents excellent reliability. We found low interrater variability (3.6%), suggesting low measurement error, and an ICC estimate of 0.63, suggesting moderate agreement.

2.7 | Analytical methods

Plasma glucose was measured in the laboratory of the Turku PET Centre in duplicate using the glucose oxidase technique (Analox GM7 or GM9, Analox Instruments, London, UK). HbA1c was measured with ion-exchange high performance liquid chromatography (Variant II HbA1c, Bio-Rad Laboratories, CA, USA). Serum insulin was determined by time-resolved immunofluorometric assay (AutoDELFIA, Perkin Elmer Life and Analytical Sciences). Serum FFA were measured with a photometric enzymatic assay (Wako Chemicals, Neuss, Germany) on a Modular P800 automatic analyser (Roche Diagnostics, Mannheim, Germany). Serum high-sensitivity C-reactive protein was analysed by the sandwich immunoassay method using an Innotrac Aio1 immunoanalyser (Innotrac Diagnostics, Turku, Finland). Serum adipokines were analysed in duplicate by using Milliplex Human Serum Adipokine (Panel A) kit (cat. no. HADK1-61 K-A) containing interleukin-6 (IL-6), IL-8, tumour necrosis factor alpha and leptin.

2.8 | Statistical analysis

Data are presented as mean ± SD (or median [IQR] for nonnormally distributed variables). Whole-brain statistical analysis was performed with statistical parametric mapping (SPM12) toolbox tuning on Matlab. Linear regressions were performed in SPM to evaluate correlations between BFAU and single regressors (BMI, OGIS, leptin, whole-body lipid oxidation, hypothalamus/amygdala signal ratio) while controlling for confounding factors (in the SPM contrast, the controlling variables were set to a value of 0). The statistical threshold in SPM analysis was set at a cluster level and corrected with false discovery rate (FDR) with $P < 0.05$. Fatty acid uptake values were extracted from nine ROIs (global, anterior cerebellum [CER-A], posterior cerebellum [CER-P], frontal lobe [FRO], limbic lobe [LIMB], midbrain [MID], occipital lobe [OCC], parietal lobe [PAR], temporal lobe [TEMP]) with Marsbar plug-in for Matlab and correlated against the selected variables using either Pearson (*r*) or Spearman (*rho*) correlation analysis, as appropriate. Further statistical analyses were performed using JMP version 13.0 (SAS Institute, Cary, NC, USA). A *P*-value <0.05 was considered statistically significant.

3 | RESULTS

3.1 | Clinical and metabolic characteristics of the study participants

HbA1c and fasting glucose were the only variables where statistically significant differences were found between T2D and nondiabetic obese participants, and for this reason the data of T2D and nondiabetic subjects were pooled for further analysis. As expected, obese participants had higher measures of adiposity (waist-to-hip ratio, fat mass, BMI), higher fasting FFA and glycerol levels, and worse insulin sensitivity, compared with age-matched lean controls. Obese participants also had high circulating inflammatory markers (Table 1).

3.2 | Before surgery

Brain FFA uptake was higher in the obese compared with lean subjects (1.12 [0.61] vs. 0.72 [0.50] µmol 100 g^{-1} min^{-1}, $P = 0.002$), globally (Figure 1), as well as in the various brain regions explored (Table 2). This increase was driven by higher FFA availability (0.80 ± 0.22 vs. 0.55 ± 0.17 mmol/L, $P = 0.001$) as the fractional uptake rates were similar in the two groups. By contrast, the FLAIR hypothalamus/amygdala signal ratio did not differ between obese and control subjects (Table 2).

TABLE 1 Clinical and metabolic characteristics of the two study groups[§]

		Obese		
	Controls (n = 14)	Before (n = 24)	After (n = 21)	P°
Age (years)	45 ± 12	43 ± 10	-	-
BMI (kg/m^2)	22.6 ± 2.8	41.1 ± 4.2*	31.8 ± 4.2#	<0.0001
WHR (cm/cm)	0.77 ± 0.05	0.89 ± 0.07*	0.87 ± 0.09#	0.04
Fat mass (kg)	19 ± 6	56 ± 10*	37 ± 9#	<0.0001
Fat-free mass (kg)	42 ± 4	56 ± 9*	49 ± 6#	<0.0001
Triglycerides (mmol L^{-1})	0.66 ± 0.32	1.18 ± 0.42*	1.09 ± 0.54#	ns
Glucose (mmol L^{-1})	5.13 ± 0.34	5.71 ± 1.03*	5.30 ± 0.79	ns
Insulin (μU mL^{-1})	3.0 [3.5]	9.5 [10.8]*	4.0 [3.0]	(0.06)
OGIS (ml min^{-1} m^{-2})	426 [91]	351 [67] *	444 [63]	<0.0001
HbA1c, % (mmol/mol)	5.6 ± 0.3 (38 ± 3)	6.0 ± 0.7 (42 ± 7)*	5.4 ± 0.4 (36 ± 5)	<0.0001
FFA (mmol L^{-1})	0.55 ± 0.17	0.80 ± 0.22*	0.77 ± 0.17#	ns
Glycerol (μmol/L)	67 ± 23	113 ± 31*	108 ± 53#	0.01
hs-CRP (mg/L)	0.4 [0.6]	2.9 [3.8]*	0.9 [1.4]#	0.003
IL-6 (pg/ml)	1.6 [2.4]	2.4 [2.4] *	1.2 [2.5]	0.02
IL-8 (pg/ml)	4.14 [1.5]	4.6 [2.6]	4.4 [2.3]	ns
TNF-α (pg/ml)	2.4 [1.8]	4.4 [1.6]*	3.7 [1.9]	0.07
Leptin (ng/ml)	5.3 [5.3]	36.8 [21.3]*	15.4 [14.2]	<0.0001

Abbreviations: BMI, body mass index; FFA, free fatty acids; hs-CRP, serum high-sensitivity C-reactive protein; IL-6, interleukin-6; IL-8, interleukin-8; ns, nonsignificant; OGIS, oral glucose insulin sensitivity; TNF-α, tumour necrosis factor alpha; WHR, waist-to-hip ratio.

[§]Data are mean ± SD or median [IQR]; *$P \leq 0.05$ obese vs. controls; °after vs. before surgery; #$P \leq 0.05$ obese after surgery vs. controls.

3.3 | After surgery

Postsurgical data were available for 21 subjects (three subjects did not undergo surgery). As expected, 6 months after the operation participants had lost a significant amount of body weight (26 ± 8 kg). Serum FFA levels were not decreased (0.80 ± 0.22 vs. 0.77 ± 0.17 mmol/L, ns), probably because of the ongoing catabolic state. As FUR was also unchanged, BFAU was not altered by surgery (Table 2 and Figure 2A). The FLAIR hypothalamus/amygdala signal ratio was also unchanged (Table 2). Insulin sensitivity (as indexed by OGIS), HbA1c levels and circulating inflammatory markers were improved (Table 1).

3.4 | Correlations

In the whole dataset, baseline BFAU was positively associated with BMI (r = 0.47, P = 0.003) and other markers of adiposity such as fat mass (r = 0.45, P = 0.006) and leptin (r = 0.54, P = 0.0008), and negatively with OGIS (r = –0.45, P = 0.007). BFAU was also directly related to whole-body lipid oxidation (r = 0.52, P = 0.001) (Figure 2B). By contrast, the FLAIR hypothalamus/amygdala signal ratio did not correlate with BMI, circulating inflammatory markers, or BFAU (Figure 3). When accounting for BMI, the correlations that remained significant were those between BFAU and leptin (P = 0.05), and between BFAU and whole-body lipid oxidation (P = 0.03).

In the 18 subjects for whom we had follow-up data, baseline BFAU predicted higher plasma glucose levels at 2 years of follow up (Figure 2C). The association remained significant after adjusting for baseline plasma glucose levels. Baseline serum FFA also predicted higher plasma glucose levels at 2 years of follow-up.

4 | DISCUSSION

Our data show that, in the postabsorptive state, morbidly obese subjects have higher BFAU compared with lean individuals, and that, 6 months after surgery, BFAU is essentially unchanged because of the ongoing catabolic state and high substrate availability. Thus, we replicate and extend our original findings in metabolic syndrome.[8]

In the postabsorptive state, increased BFAU in the obese results from high substrate (circulating FFA) availability because there is no difference in the intrinsic avidity of the brain for FFA (as reflected by the fractional uptake rate). Thus, although the increased BFAU of the obese seems to be an epiphenomenon of their metabolic status (excess lipolysis, because of insulin resistance), the chronic excess of fatty acid supply could ultimately lead to central deleterious effects and, eventually, deterioration of their metabolic health. Indeed, in the current data, baseline BFAU predicted worse plasma glucose levels at 2 years of follow-up. This is consistent with our previous finding in morbidly obese subjects undergoing bariatric surgery studied with [^{18}F]-

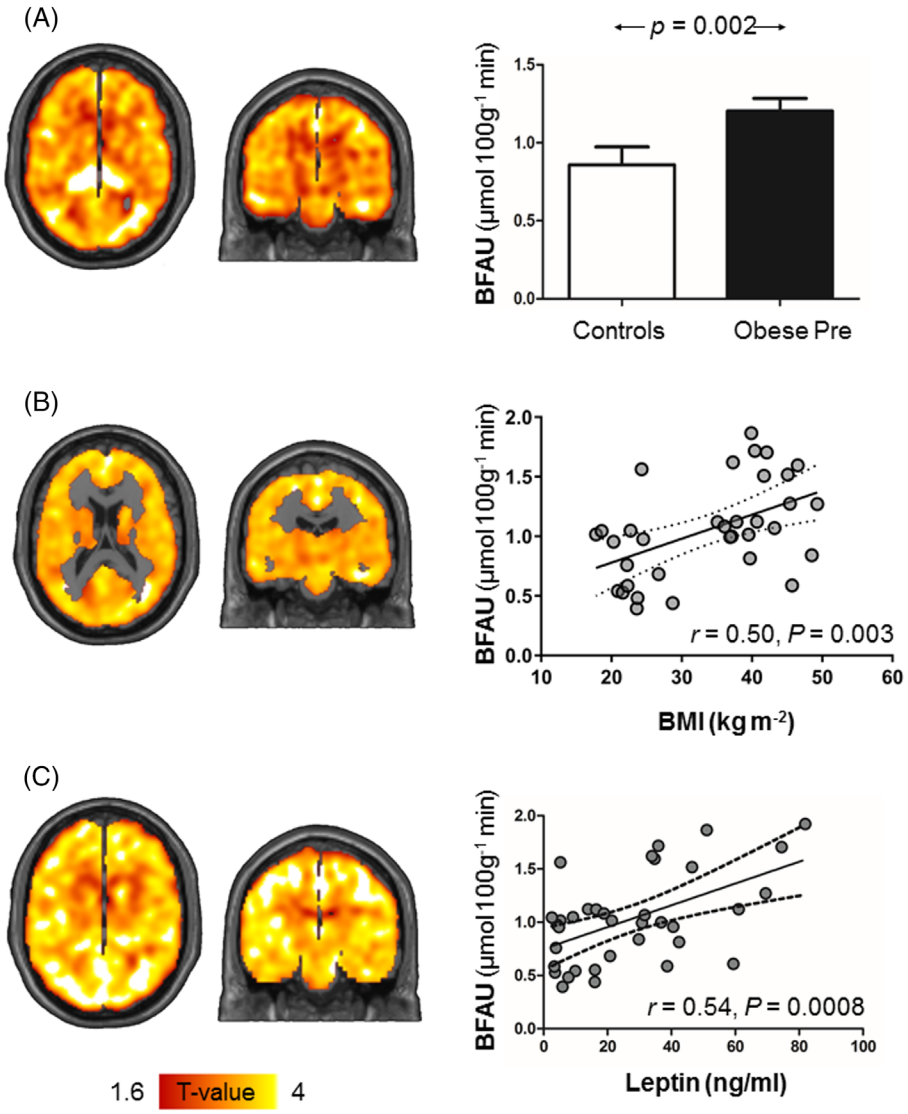

FIGURE 1 Brain clusters (as defined by false discovery rate [FDR]-corrected statistical parametric mapping [SPM] one-sample *t*-test) for the comparison of brain fatty acid uptake (BFAU) between the two groups, and the corresponding bar graphs (A). Brain clusters for the association between BFAU and (B) body mass index (BMI) and (C) circulating leptin levels (C). For the corresponding bar graphs and scatterplots, the global region of interest (ROI) was extracted and used

TABLE 2 Brain fatty acid uptake and FLAIR hypothalamus/amygdala signal ratio[§]

		Obese		
	Controls (n = 14)	Before (n = 24)	After (n = 21)	*P*[*]
Global (µmol/100 g/min)	0.72 [0.50]	1.12 [0.61]	1.09 [0.39][#]	0.002
Cerebellum anterior (µmol/100 g/min)	0.77 [0.57]	1.32 [0.75]	1.21 [0.49][#]	0.001
Cerebellum posterior (µmol/100 g/min)	0.75 [0.61]	1.19 [0.73]	1.13 [0.48]	0.006
Frontal lobe (µmol/100 g/min)	0.67 [0.50]	1.04 [0.55]	0.99 [0.34] [#]	0.002
Limbic lobe (µmol/100 g/min)	0.71 [0.48]	1.11 [0.61]	1.06 [0.45] [#]	0.002
Midbrain (µmol/100 g/min)	0.75 [0.52]	1.21 [0.71]	1.12 [0.42] [#]	0.002
Occipital lobe (µmol/100 g/min) (µmol/100 g/min)	0.79 [0.55]	1.21 [0.65]	1.17 [0.40] [#]	0.003
Parietal lobe (µmol/100 g/min)	0.75 [0.53]	1.17 [0.64]	1.14 [0.39] [#]	0.001
Temporal lobe (µmol/100 g/min)	0.72 [0.48]	1.09 [0.58]	1.05 [0.38] [#]	0.002
Hypothalamus/amygdala signal ratio	1.07 [0.04]	1.07 [0.08]	1.07 [0.09]	ns

Abbreviations: FLAIR, fluid-attenuated inversion recovery; ns, nonsignificant.

[§]Data are median [IQR]; *obese vs. controls; ◦*P* ≤ 0.05 after vs. before surgery; #*P* ≤ 0.05 obese after surgery vs. controls.

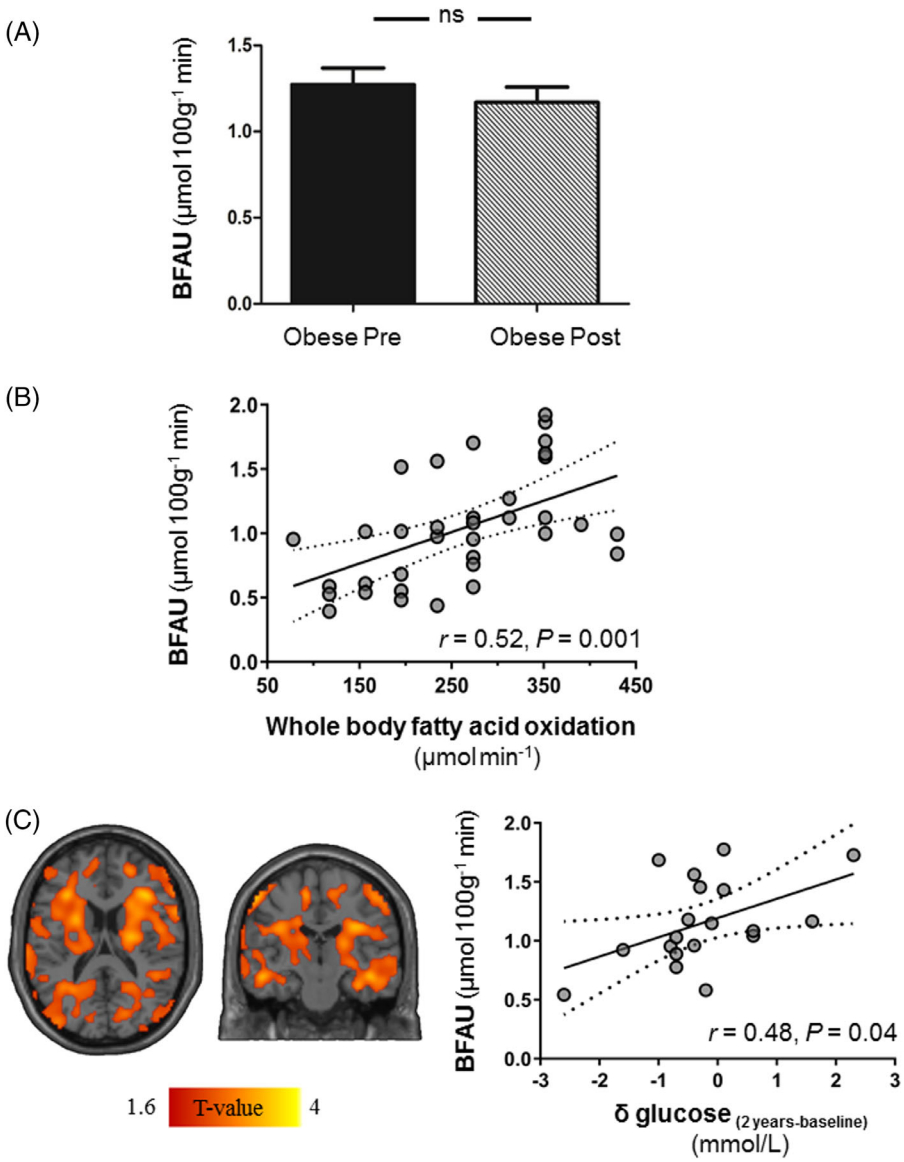

FIGURE 2 (A) No difference in brain fatty acid uptake (BFAU) was found 6 months after bariatric surgery. (B) Brain clusters for the association between BFAU and whole-body lipid oxidation. (C) Brain clusters for the association between BFAU and the change in plasma glucose at 2 years of follow-up and the corresponding scatterplot; ns, nonsignificant

fluorodeoxyglucose-PET under euglycaemic hyperinsulinemic conditions, where higher brain glucose uptake also predicted worse glycaemic levels at 2 and 3 years of follow-up.[17] Taken together, these and other findings[18] indicate that in humans brain substrate handling may be involved in the control of whole-body homeostasis.

A well-described central effect of FFA is the induction of hypothalamic inflammation.[19] Assessing hypothalamic inflammation in vivo in humans is demanding. One method that has been proposed to depict hypothalamic inflammation is the T2 hypothalamic/amygdala hyperintensity signal. However, as previously argued,[4] this signal does not constitute definitive proof of increased gliosis, as infection, oedema and tumours may have a similar appearance. We therefore analysed FLAIR-MRI data (a similar to T2 MRI sequence optimal in analysing small periventricular areas) to test whether brain FFA uptake would correlate with the hypothalamic/amygdala hyperintensity signal. Contrary to expectations, we found no such correlations. In addition, despite separate analysis of the FLAIR-MRI data by two expert neuroradiologists, we also failed to replicate previous findings,[4,9,10] that is, correlations of this ratio with BMI or inflammatory markers. This discrepancy may in part be explained by technical reasons. The hypothalamus is a very small brain region, and our FLAIR-MRI sequence was protocoled to cover the whole brain with 5 mm-thick slices. These comparatively thick slices may have caused ROI malpositioning, and preclude sensitivity for subtle changes in hypothalamic FLAIR signal. We found small measurement error (inter-rater variability), yet only moderate intraclass correlations (0.63). Previous studies have not assessed the reliability of hypothalamic FLAIR measurements. This pattern of results suggests insufficient between-subject variability (ie, identifiability of individuals) to make this ratio an optimal biomarker in metabolic studies. Therefore, further studies with advanced techniques are necessary to assess whether central inflammation occurs in human obesity and whether it is improved following bariatric surgery.

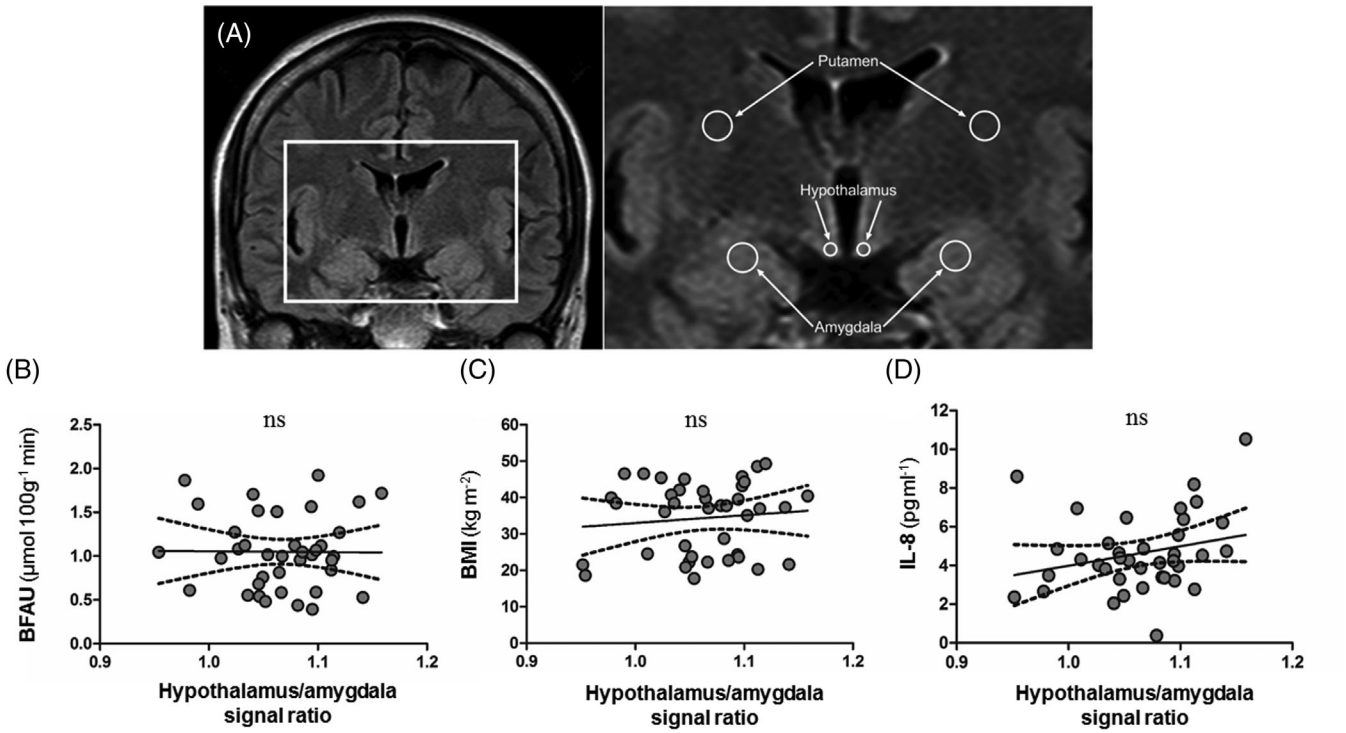

FIGURE 3 (A) Representative coronal fluid-attenuated inversion recovery (FLAIR) image through the hypothalamus. The zoomed image on the right shows the placement of right and left regions of interest (ROIs) in the hypothalamus, amygdala and putamen. Lack of correlation between the FLAIR hypothalamus/amygdala signal ratio and (B) brain fatty acid uptake (BFAU), (C) body mass index (BMI) and (D) circulating IL-8; IL-8, interleukin-8; ns, nonsignificant

The brain has been long considered not to use FFA. However, this notion has been challenged.[5,8] Using the palmitate analogue [^{18}F]-FTHA, we found that brain FFA uptake ranged from 0.3–1.3 μmol 100 mL^{-1} min^{-1}, which translates to a whole-brain uptake of 4–14 μmol min^{-1}. By comparison with previous PET studies using [^{18}F]-FTHA,[20-23] the brain has a comparatively high tissue-specific FFA uptake (fourth after liver, kidney and heart but higher than adipose tissue or resting skeletal muscle). Thus, brain FFA uptake makes a small contribution to whole-body FFA disposal but avidly extracts FFA from the plasma. In brain slice cultures, polyunsaturated fatty acid species (PUFA) are taken up preferentially.[6] [^{18}F]-FTHA has no double bonds, and therefore behaves as a saturated fatty acid. Consequently, we cannot out rule out that BFAU would have been higher had it been measured with a PUFA analogue. Unfortunately, thus far, such a tracer is not available.

With regard to the intracellular fate of fatty acids in the brain, preclinical studies have shown that the only brain cell type capable of oxidizing fatty acids is the astrocytes.[5] Astrocytes also contain lipid droplets, which can be released as exosomes and subsequently taken up by neurons[7] for their structural needs. In the postabsorptive state, one could hypothesize that substrate uptake would be at least in part directed to oxidation and energy production. In their elegant review, Schönfeld and Reiser[24] conclude that activated fatty acids can be either esterified to membrane lipids or undergo β-oxidation in the mitochondria, and argue that excessive oxidation of fatty acids could be detrimental for the "economy" of the brain cells. Accordingly, our previous study using both [^{18}F]-FTHA-PET and [^{11}C]-palmitate-PET (the former tracking total FFA uptake, the latter nonoxidative metabolism) concluded that not all of the fatty acids are oxidized by the brain.[8]

The current results show group differences (obese vs. lean participants), correlations (between BFAU and brain-derived or metabolic variables), and the effect of bariatric surgery. The mechanistic background of these findings has not been specifically addressed but some clues help in formulating a mechanistic hypothesis, for example, the strong association of BFAU with leptin. Leptin is an adipokine that crosses the blood–brain barrier and acts as a neuropeptide in the brain. Astrocytes, which have been identified as key metabolic players, express the leptin receptor in obesity.[25] Chronic exposure to leptin by intracerebroventricular application has been shown to increase the expression of glial fibrillary acidic protein and vimentin, and to increase the expression of astrocyte structural proteins.[26] The chronic hyperleptinaemia of the obese leading to astrocyte activation might be the origin of the observed increase in BFAU. Future preclinical studies could compare BFAU in wild type and leptin-deficient rats.

Our study has limitations. First, we only included women, so extrapolation of our findings to men should be conducted with caution. Second, because of the physics of the PET, small anatomical regions such as the hypothalamus could not be analysed with sufficient resolution.[27] Third, we used MRI to probe central nervous

system inflammation. Although the analysis was performed by two independent researchers, with good agreement values between them, MRI may not be the optimal technique with which to detect brain inflammation.

In summary, morbidly obese subjects have a higher BFAU compared with lean individuals. BFAU is essentially unchanged after surgically induced major weight loss, probably because of the ongoing catabolic state and high substrate availability. Baseline BFAU predicts worse plasma glucose levels at follow-up, supporting the notion that the brain participates in the control of whole-body glucose homeostasis.

ACKNOWLEDGMENTS

The authors thank the staff of the Turku PET Centre for performing the PET imaging. The authors also thank the research nurse, Mia Koutu, of Turku PET Centre, for data collection.

This study was conducted within the Center of Excellence in Cardiovascular and Metabolic Diseases, supported by the Academy of Finland (grant 307402), the University of Turku, Turku University Hospital, Åbo Akademi University, Finnish Diabetes Foundation, and Sigrid Juselius Foundation.

Parts of this study were presented as an abstract at the 55th EASD annual meeting in Berlin in September, 2019.

CONFLICT OF INTEREST

No potential conflicts of interest relevant to this article were reported.

AUTHOR CONTRIBUTIONS

E.R., J.H., M.B., L.P., M.N., J.C.H. and L.N. analysed data and literature and drafted the manuscript. J.C.H. conducted the clinical PET studies. J.H. and M.N. performed the FLAIR analysis. P.S. operated on the patients. P.I., L.N. and P.N. conceived the study designs. P.I., L.N., E.F. and P.N. reviewed the manuscript. All authors approved the final version of the manuscript.

P.N. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

ORCID

Eleni Rebelos https://orcid.org/0000-0003-3050-8692
Ele Ferrannini https://orcid.org/0000-0002-1384-1584
Pirjo Nuutila https://orcid.org/0000-0001-9597-338X

REFERENCES

1. World Health Organization. *Obesity and overweight*. Geneva, Switzerland: World Health Organization; 2018.
2. Pugazhenthi S, Qin L, Reddy PH. Common neurodegenerative pathways in obesity, diabetes, and Alzheimer's disease. *Biochim Biophys Acta Mol Basis Dis*. 1863;2017:1037-1045.
3. Hotamisligil GS. Inflammation and metabolic disorders. *Nature*. 2006; 444:860-867.
4. Thaler JP, Yi CX, Schur EA, et al. Obesity is associated with hypothalamic injury in rodents and humans. *J Clin Invest*. 2012;122:153-162.
5. Edmond J, Robbins RA, Bergstrom JD, Cole RA, de Vellis J. Capacity for substrate utilization in oxidative metabolism by neurons, astrocytes, and oligodendrocytes from developing brain in primary culture. *J Neurosci Res*. 1987;18:551-561.
6. Hofmann K, Rodriguez-Rodriguez R, Gaebler A, Casals N, Scheller A, Kuerschner L. Astrocytes and oligodendrocytes in grey and white matter regions of the brain metabolize fatty acids. *Sci Rep*. 2017;7: 10779.
7. Falchi AM, Sogos V, Saba F, Piras M, Congiu T, Piludu M. Astrocytes shed large membrane vesicles that contain mitochondria, lipid droplets and ATP. *Histochem Cell Biol*. 2013;139:221-231.
8. Karmi A, Iozzo P, Viljanen A, et al. Increased brain fatty acid uptake in metabolic syndrome. *Diabetes*. 2010;59:2171-2177.
9. Schur EA, Melhorn SJ, Oh SK, et al. Radiologic evidence that hypothalamic gliosis is associated with obesity and insulin resistance in humans. *Obesity (Silver Spring)*. 2015;23:2142-2148.
10. Kreutzer C, Peters S, Schulte DM, et al. Hypothalamic inflammation in human obesity is mediated by environmental and genetic factors. *Diabetes*. 2017;66:2407-2415.
11. Helmio M, Victorzon M, Ovaska J, et al. SLEEVEPASS: a randomized prospective multicenter study comparing laparoscopic sleeve gastrectomy and gastric bypass in the treatment of morbid obesity: preliminary results. *Surg Endosc*. 2012;26:2521-2526.
12. Report of the expert committee on the diagnosis and classification of diabetes mellitus. *Diabetes Care*. 2003;26(Suppl 1):S5-S20.
13. Honka H, Koffert J, Hannukainen JC, et al. The effects of bariatric surgery on pancreatic lipid metabolism and blood flow. *J Clin Endocrinol Metab*. 2015;100:2015-2023.
14. Patlak CS, Blasberg RG. Graphical evaluation of blood-to-brain transfer constants from multiple-time uptake data. *Generalizations J Cereb Blood Flow Metab*. 1985;5:584-590.
15. Schrauwen P, Wagenmakers AJ, van Marken Lichtenbelt WD, Saris WH, Westerterp KR. Increase in fat oxidation on a high-fat diet is accompanied by an increase in triglyceride-derived fatty acid oxidation. *Diabetes*. 2000;49:640-646.
16. Mari A, Pacini G, Murphy E, Ludvik B, Nolan JJ. A model-based method for assessing insulin sensitivity from the oral glucose tolerance test. *Diabetes Care*. 2001;24:539-548.
17. Rebelos E, Immonen H, Bucci M, et al. Brain glucose uptake is associated with endogenous glucose production in obese patients before and after bariatric surgery and predicts metabolic outcome at follow-up. *Diabetes Obes Metab*. 2019;21:218-226.
18. Tschritter O, Preissl H, Hennige AM, et al. High cerebral insulin sensitivity is associated with loss of body fat during lifestyle intervention. *Diabetologia*. 2012;55:175-182.
19. Dalvi PS, Chalmers JA, Luo V, et al. High fat induces acute and chronic inflammation in the hypothalamus: effect of high-fat diet, palmitate and TNF-alpha on appetite-regulating NPY neurons. *Int J Obes (Lond)*. 2017;41:149-158.
20. Dadson P, Ferrannini E, Landini L, et al. Fatty acid uptake and blood flow in adipose tissue compartments of morbidly obese subjects with or without type 2 diabetes: effects of bariatric surgery. *Am J Physiol Endocrinol Metab*. 2017;313:E175-E182.
21. Immonen H, Hannukainen JC, Kudomi N, et al. Increased liver fatty acid uptake is partly reversed and liver fat content normalized after bariatric surgery. *Diabetes Care*. 2018;41:368-371.
22. Rebelos E, Dadson P, Oikonen V, et al. Renal hemodynamics and fatty acid uptake: effects of obesity and weight loss. *Am J Physiol Endocrinol Metab*. 2019;317:E871-E878.
23. Hannukainen JC, Lautamaki R, Parkka J, et al. Reversibility of myocardial metabolism and remodelling in morbidly obese patients 6 months after bariatric surgery. *Diabetes Obes Metab*. 2018;20: 963-973.
24. Schonfeld P, Reiser GJ. Why does brain metabolism not favor burning of fatty acids to provide energy? - Reflections on disadvantages of the use of free fatty acids as fuel for brain. *Cereb Blood Flow Metab*. 2013;33:1493-1499.

25. Hsuchou H, He Y, Kastin AJ, et al. Obesity induces functional astrocytic leptin receptors in hypothalamus. *Brain*. 2009;132:889-902.
26. Garcia-Caceres C, Fuente-Martin E, Burgos-Ramos E, et al. Differential acute and chronic effects of leptin on hypothalamic astrocyte morphology and synaptic protein levels. *Endocrinology*. 2011;152:1809-1818.
27. Teräs M. *Performance and methodological aspects in positron emission tomography*. Turun Yliopisto: Turku, Finland; 2008.

How to cite this article: Rebelos E, Hirvonen J, Bucci M, et al. Brain free fatty acid uptake is elevated in morbid obesity, and is irreversible 6 months after bariatric surgery: A positron emission tomography study. *Diabetes Obes Metab*. 2020;1–9. https://doi.org/10.1111/dom.13996