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Increased brain fractional perfusion in obesity using intravoxel incoherent motion (IVIM) MRI metrics

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Abstract

Objective: This research seeks to shed light on the associations between brain perfusion, cognitive function, and mental health in individuals with and without obesity.

Methods: In this study, we employed the noninvasive intravoxel incoherent motion (IVIM) magnetic resonance imaging (MRI) technique to examine brain fractional perfusion (FP) in two groups: individuals with obesity ($N = 72$) and healthy controls ($N = 66$). Additionally, we investigated potential associations between FP, cognitive function, and depressive symptoms in the participants with and without obesity. Finally, artificial intelligence algorithms (Boruta analysis) were also used.

Results: Participants with obesity exhibited increased FP within dopaminergic brain circuits, particularly involving prefrontal cortex areas, anterior and posterior sections of the cingulate cortex, the right striatum, and the midbrain. Additionally, these individuals demonstrated lower working memory and higher depressive symptoms compared to the control group. Notably, higher FP in the inferior temporal and occipital cortices correlated with greater depressive symptoms, whereas increased FP in the right ventral caudate and the midbrain was associated with better working memory performance. A link between inflammatory and metabolic variables, with a particular emphasis on monocytes, and FP in obesity was also evidenced by Boruta analysis.

Anna Motger-Albertí and Elena Calle contributed equally to the work.

Conclusions: Increased brain perfusion in individuals with obesity is associated with cognitive function and mental health through interaction with metabolic and inflammatory factors.

INTRODUCTION

Obesity is a global public health problem with serious physical, cognitive, and psychological health implications [1–6]. Obesity has been associated with decreased white matter microstructure [1]; brain atrophy in the frontal lobes, anterior cingulate gyrus, hippocampus, and thalamus [2]; and altered brain function [3].

Obesity-related cerebral perfusion alterations have been the subject of intense research in recent years. Most previous studies assessing cerebral perfusion in people with obesity have reported a pattern of whole [4, 5] or regional [4, 6] brain hypoperfusion, with isolated findings of both increases and decreases [6], or no effects [7]. However, the current overview of cerebral perfusion in people with obesity is still scarce and mainly based on invasive imaging techniques, with challenges including cost, availability, low resolution, and nonspecific radiotracer binding [8]. The findings have been heterogeneous for several reasons: (a) the use of different types of techniques (positron emission tomography [PET] [8], photon emission computed tomography [SPECT] [9], arterial spin labeling [ASL] perfusion [4, 5, 8] transcranial doppler sonography [TDS] [10]); (b) the variety of age ranges (young [4], adult elderly [5]); (c) studies of women [9]; (d) samples with important cardiovascular, type 2 diabetes mellitus, and neurological comorbidities [6]; (e) the use of different body mass index (BMI) thresholds for the definition of obesity (≥ 26 kg/m^2 [4], ≥ 30 kg/m^2 [6, 9], ≥ 35 kg/m^2 [7]); and (f) the different approaches to study cerebral perfusion (global gray matter cerebral blood flow measure [4], whole brain maps [7], voxel-wise approaches [4, 6, 9]).

The intravoxel incoherent motion (IVIM)-based perfusion magnetic resonance imaging (MRI) technique approach [11, 12] is a new modality for studying cerebral perfusion that does not require contrast agents and has more advanced modeling than diffusion studies. IVIM has been used to study tumors [13–15], neurological and cardiovascular diseases [15], and neurodegenerative processes like Alzheimer's disease (AD) [16, 17].

This study uses IVIM to investigate changes in cerebral perfusion in people with obesity compared to a control group, as well as the association between the identified changes, attentional and working memory processes, and depressive symptoms in each group. We also explored the importance of inflammatory variables and metabolic markers on brain perfusion changes.

Study Importance

What is already known?

- The current understanding of cerebral perfusion in individuals with obesity remains uncertain, mainly due to reliance on invasive imaging techniques, leading to inconsistent results. To address this gap, this study employs a noninvasive technique called intravoxel incoherent motion (IVIM) to investigate variations in cerebral perfusion between individuals with obesity and a control group. Additionally, the study explores the correlation between these perfusion changes and cognitive function as well as depression symptoms, metabolic markers, and inflammatory factors.

What does this study add?

- Participants with obesity exhibited increased brain fractional perfusion (FP) within dopaminergic brain circuits, particularly involving prefrontal cortex areas. Additionally, these individuals demonstrated lower working memory and higher depressive symptoms compared to the control group. A link between brain FP in obesity and inflammatory and metabolic variables was also evidenced.

How might these results change the direction of research or the focus of clinical practice?

- The research findings indicated a link between inflammatory and metabolic variables, with a particular emphasis on monocytes, and brain FP in obesity.
- Scrutinizing cerebral perfusion in different stages of metabolic disease can help identify individuals with a relatively greater need for obesity intervention.

METHODS

Participants

The sample included 72 individuals with obesity (BMI ≥ 30 kg/m^2) and 66 healthy controls (HCs) (68.8% women). People with obesity were consecutively recruited at the Endocrinology Department of Josep Trueta University Hospital (Girona, Spain) and HCs through advertisements and word-of-mouth. Eligible participants were between 30 and 65 years old. Exclusion criteria for the study participants included (i) presence of current or past medical illness (e.g., type 2 diabetes mellitus, cancer, inflammatory-related illnesses) or disabling psychiatric disorders (e.g., moderate–severe psychiatric disorders); (ii) language disorders, neurological diseases, or history of trauma or brain injury; (iii) acute or chronic heavy alcohol consumption (i.e., ≥40 g OH/day in women or ≥ 80 g OH/day in men); (iv) clinical symptoms and signs of infection in the previous month or antibiotic,

antifungal, or antiviral treatment in the previous 3 months; (v) pregnancy and/or lactation; and (vi) MRI contraindications (e.g., claustrophobia, ferromagnetic implants).

The study protocol was approved by The Institutional Review Board-Ethics Committee and the Committee for Clinical Research at the Josep Trueta University Hospital. All procedures were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. All participants gave written informed consent to participate in the study.

Clinical measurements

BMI was estimated by using the participants' weight (kilograms) and height (meters) (BMI = weight/[height]^2). Participants with BMI ≥ 30 were considered as having obesity. Fat mass was assessed using dual-energy x-ray absorptiometry (GE Lunar, Madison, Wisconsin). Menopausal status was registered in each woman and defined as the absence of menses for at least 1 year.

Monocytes, fasting plasma glucose, insulin in serum, erythrocyte sedimentation rate (mm 1st hour), total white blood cells (WBC), hemoglobin, aspartate aminotransferase, alanine aminotransferase, gamma-glutamyltransferase, lipid profiles (i.e., cholesterol [total, high-density lipoprotein, and low-density lipoprotein cholesterol], triglycerides, glucose, uric acid, urea), ferritin, and high-sensitivity C-reactive protein (hsCRP) were measured using an analyzer (Cobas 8000 c702, Roche Diagnostics, Basel, Switzerland). Glycated hemoglobin (HbA1c) was determined by high-performance liquid chromatography (HPLC; ADAM A1c HA-8180 V, ARKRAY, Inc., Kyoto, Japan). Systolic and diastolic blood pressure and pulse were also measured.

Neuropsychology assessment

Attention and executive function

The total digit span test (TDS) is a component of the Wechsler Adult Intelligence Scale (WAIS-III). It is composed of two parts: forward and backward digit span tests. In the forward digit span test, the participant repeats a series of numbers in the same order that was presented initially. In the backward digit span exercise, the participant repeats a series of progressively longer digits in reverse order. The total digit span is calculated by adding together the two assignments. A higher score indicates better attention and working memory.

Depressive symptoms

The Patient Health Questionnaire (PHQ-9) is a self-administered questionnaire containing nine items of depression symptomatology from the previous 2 weeks, with Likert-type responses with values ranging from 0 to 3. After adjustment, a total score that runs from 0 to 27 is produced after adjustment. The suggested cutoffs are minimal depression (1–4), mild depression (5–9), moderate depression (10–14), moderately severe depression (15–19), and severe depression (19+) [18].

MRI acquisition and processing

All participants were assessed on a 1.5-T Ingenia system (Philips Healthcare, Best, the Netherlands) with 15-channel head coils. Participants underwent a diffusion weighted imaging (DWI)-IVIM sequence (single-shot echo planar imaging [EPI] sequences, with six different *b* values from 0 to 4000 s/mm^2 [0–200–500–1000–2500–4000]), with a parallel imaging sensitivity encoding (SENSE) scheme acceleration factor of 2 (repetition time [TR] = 3352 ms, echo time [TE] = 97 ms, field of view [FOV] = 23,0230 pixel matrix, voxel size 2 mm^3 × 2 mm^3 × 5 mm^3, 22 sections, 2 min 5 s acquisition time), and a T1-weighted anatomical scan (TR = 8.3 ms, TE = 4.1 ms, flip angle = 8°, FOV = 230 mm × 190 mm, 232 × 229 pixel matrix, section thickness = 1 mm).

The DWI-IVIM sequence was processed and analyzed using MATLAB version R2017a (The MathWorks, Inc., Natick, Massachusetts) and Statistical Parametric software (SPM12; The Wellcome Department of Imaging Neuroscience, London, UK). Philips IntelliSpace Portal was used to check the image quality, correct signal, and motion distortions. Fractional perfusion (FP) scalar maps were subsequently computed from the DWI-IVIM sequence. Skull stripping method by the Brain Extraction Tool was also performed on these images. Then, spatial normalization was performed using in-house templates of each parametric map made from a representative healthy cohort and registered to the standard SPM template to 2-mm resolution. All DWI-IVIM maps were smoothed with an 8-mm full-width at half-maximum isotropic gaussian kernel.

The T1-weighted sequence was analyzed using Freesurfer software v6 (Athinoula A. Martinos Center for Biomedical Imaging, Charlestown, Massachusetts; http://surfer.nmr.mgh.harvard.edu/) with the recon-all function [19]. The images were parcellated with the Aseg atlas [20]. This scan was used for anatomical reference and to calculate total intracranial and gray matter volumes.

Statistical analysis

The comparison between sociodemographic, clinical, and neuropsychological variables between the study groups, as well as the implementation of Boruta analyses, was performed in R version 4.2.2 in R Studio. Brain image analyses with the DWI-IVIM maps (i.e., between-group differences in brain FP and associations with neuropsychological variables) were performed using the CONN functional connectivity [21] toolbox.

Sociodemographic, clinical, neuropsychological, and volumetric measures

Differences in sociodemographic, clinical, and neuropsychological features (raw scores) were expressed as percentage and frequency for categorical variables, mean ± standard deviation (SD) for continuous variables, and median and interquartile range (IQR) for non-normally distributed continuous variables. Statistical significance of differences between groups was calculated according to normality and homoscedasticity assumptions: *t* test for normal distribution and nonparametrical Wilcoxon rank sum test for non-normal distribution. For categorical variables, Pearson χ^2 test with Yates continuity correction was used. For volumetric MRI, measures were determined using Wilcoxon rank sum test for non-normal quantitative distributed variables and unpaired Student *t* test for normal quantitative variables. Results are expressed as number and frequency for categorical variables, mean ± SD for normal distributed continuous variables, and median and IQR for non-normal distributed continuous variables.

Brain FP analyses

We analyzed between-group differences on brain FP using a two-sample Student *t* test. This model was repeated while including pulse pressure as a confounder variable [22]. In addition, because of the evidence linking the menopausal status with brain circulation [23, 24] we ran a new two-sample Student *t* test to compare FP between the pre- and postmenopausal females in the study. The association between FP and the neuropsychological variables and depressive symptoms in each of the study groups was then assessed using linear regression models. All these analyses were adjusted for age, sex, education, and alcohol intake. Significance thresholding for these image analyses was determined through parametric statistics based on gaussian random field theory [25], setting statistical significance thresholds of 0.001 uncorrected *p* value for voxel threshold and $p < 0.05$ false discovery rate (FDR)-corrected for cluster threshold. We additionally explored for specific associations with subcortical brain regions showing between-group differences in perfusion using small volume procedures ($p_{FWE\text{-}SVC} < 0.05$ corrected for multiple comparisons across all within-mask voxels inside a 3.5-mm sphere located in the peak coordinates).

Boruta algorithm

We used an artificial intelligence algorithm (the Boruta analysis) to identify clinical variables associated with the FP derived from all the brain regions showing a significant difference between the groups (mean residual value from the voxels of brain regions in Table 2 that fall inside a gray matter mask). The Boruta algorithm is a wrapper algorithm that selects feature according to the model's learning performance [26]. It performs variables selection in three steps: (a) randomization, to create a duplicate copy of the original features, randomly permutates across the observations; (b) model building, based on RF with the extended data set, to compute the normalized permutation variable importance measure (VIM) scores; (c) statistical testing, to find relevant features with a VIM higher than the best randomly permutated variables using a Bonferroni-corrected two-tailed binomial test; and (d) iteration, until the status of all features is decided. We ran the Boruta algorithm with 1000 iterations, a confidence level cutoff of 0.005 for the Bonferroni-adjusted *p* values, 5000 trees to grow the forest (ntree), and a number of features randomly sampled at each split given by the rounded down number of features/3 (the mtry recommended for regression). The algorithm was run for the whole cohort and for control and obesity groups separately. Only complete observations were required for these models; thus, we included 46 and 62 participants for control and obesity groups, respectively, who had measurements for all the clinical variables under study. To determine the directionality of the identified contributing variables, we assessed linear associations between them and the mean residual FP signal computing Pearson correlations.

RESULTS

Sociodemographic, clinical, neuropsychological, and volumetric measures

Table 1 details the sociodemographic, clinical, and cognitive characteristics of study participants. Groups differed in education, with HCs showing significantly more years of education. As expected, the groups showed significant differences in most clinical variables. Intracranial and gray matter volumes of both groups were equivalent. Participants with obesity performed statistically worse on the digit span test and scored higher on depressive symptoms than those without obesity.

FP in obesity and associations with neuropsychological variables

The regions with statistically significant differences in FP between groups are summarized in Table 2 and Figure 1. Participants with obesity had significantly higher FP in ventromedial and lateral parts of the prefrontal cortex (PFC), including the right middle and frontal gyri, ventromedial and bilateral orbital sections, and the right frontal pole. Increased FP in this group was also present in anterior (i.e., subgenual) and posterior sections of the cingulate cortex, as well as in pre- and postcentral gyri. At the subcortical level, the group with obesity demonstrated increased FP in the right striatum, which included the nucleus accumbens and the putamen and extended to the ipsilateral insula, as well as in the midbrain near the substantia nigra. These results remained virtually unchanged when estimates of pulse pressure were entered as a confounding covariate in the model, and nonsignificant differences in FP emerged in the direct comparison between the pre- and postmenopausal females in the study. The

TABLE 1 Demographic, clinical, and cognitive characteristics of the study participants.

	N	Without obesity	*N*	With obesity	*p*
Sociodemographic variables					
Age (y)	66	51.34 (40.8175, 59.0375)	72	48.17 (41.31, 53.655)	0.1254
Sex: women, %	66	31.16	71	37.68	0.4765
Education (y)	66	15 (12, 17)	72	12 (9.75, 15)	5.87E-05
Menopause: postmenopause, % women	43	53.49	52	44.23	0.4886
Tobacco, %[a]	66		72		0.7761
Nonsmoker		53.03		54.17	
Former smoker		36.36		31.94	
Current smoker		10.61		13.89	
Alcohol (g/d)	66	2.315 (0.57, 7.37)	72	0 (0, 2.345)	2.74E-05
Laboratory variables					
BMI (kg/m^2)	66	24.9364 ± 2.6179	72	43.1022 ± 6.3153	4.26E-24
Waist circumference (cm)	66	89.4697 ± 9.8344	70	125.9714 ± 14.3769	6.76E-23
Total fat (%)	65	31.9738 ± 7.2398	68	50.6 (48.125, 53.6)	8.25E-22
Android fat (%)	65	32.3585 ± 10.2794	68	57.0206 ± 5.1869	1.19E-22
Gynoid fat (%)	65	36.5 (27.7, 41.9)	68	52.5 (48.775, 55.475)	4.78E-19
SBP (mm Hg)	66	125.7273 ± 15.8973	72	137.1528 ± 19.4984	2.30E-04
DBP (mm Hg)	66	72.4545 ± 10.5934	72	76.8472 ± 11.2696	0.0197
Pulse (beats/min)	66	67.9697 ± 11.229	72	75.625 ± 9.6333	3.62E-05
Glucose (mg/dL)	66	93.5 (89, 100)	72	96.59 ± 12.164	0.2486
Insulin in serum (μIU/mL)	52	8.962 ± 4.9492	68	25.46 (18.2105, 30.3448)	5.09E-15
Cholesterol (mg/dL)	66	202.1061 ± 39.2911	72	191.5 (159.75, 219)	0.1172
LDL-cholesterol (mg/dL)	66	121.2879 ± 33.4479	72	117 (95.25, 145.5)	0.8064
HDL-cholesterol (mg/dL)	66	61 (51, 77)	72	51.375 ± 12.5568	4.56E-06
Total bilirubin (mg/dL)	65	0.47 (0.34, 0.58)	72	0.405 (0.3275, 0.5225)	0.0781
Aspartate aminotransferase (U/L)	63	20 (17, 23)	69	19 (16, 23)	0.2820
Alanine aminotransferase (U/L)	65	17 (14, 22)	72	22 (17.75, 27.25)	0.0013
Gamma-glutamyltranferase (U/L)	65	16 (12, 24)	72	23 (18, 32)	2.23E-04
Erythrocyte sedimentation rate (mm 1st hour)	63	9 (7, 16.5)	72	19 (9, 35)	4.08E-05
Hemoglobin (g/dL)	65	13.9169 ± 1.2584	72	13.8028 ± 1.3756	0.6128
Total WBC (K/μL)	65	5130 (4680, 6100)	72	7012.4806 ± 2047.6404	3.70E-08
Ferritin (ng/mL)	66	85.5 (45.25, 186)	72	82.5 (38.75, 145.25)	0.4531
Ultrasensitive CRP (mg/dL)	65	0.66 (0.4, 1.59)	70	4.985 (2.8475, 8.62)	4.02E-15

TABLE 1 (Continued)

	N	Without obesity	*N*	With obesity	*p*
Monocytes (K/μL)	65	400 (400, 500)	72	500 (400, 600)	0.0030
Urea (mg/dL)	66	33.8788 ± 7.1801	72	33 (28, 39.5)	0.7946
Creatinine (mg/dL)	66	0.8 (0.72, 0.9)	72	0.7486 ± 0.1397	0.0051
Uric acid (mg/dL)	66	4.4197 ± 1.3364	71	5.2 (4.8, 6.15)	1.85E-06
Triglycerides (mg/dL)	66	79.5 (58.5, 97.75)	72	115.5 (81.75, 148.5)	3.13E-04
Treatments, %					
Hypertension therapy	66	4.55	72	25.00	1.91E-03
Diabetes therapy	66	0	72	1.39	1.0000
Dyslipidemia therapy	66	9.09	72	12.50	0.7122
Antidepressant therapy	66	9.09	72	34.72	6.74E-04
Anxiety therapy	66	9.09	72	10.14	0.1379
Volumetric MRI measures					
Total intracranial volume (cm^3)	66	1343.0443 (1261.3089, 1461.6941)	72	1351.3233 ± 130.7402	0.3973
Total gray matter volume (cm^3)	66	512.9236 (483.9385, 559.1473)	72	504.9924 ± 35.7485	0.0876
Neuropsychological tests (raw scores)					
Digit span test					
Forward	66	9 (8, 11)	72	7.5 (6, 9)	5.92E-04
Backward	66	7 (5, 8)	72	6 (5, 7)	0.0042
Total	66	15.8485 ± 3.6679	72	13 (11, 16)	4.92E-04
PHQ-9	66	3.5 (2, 6)	72	7 (4, 10.25)	4.80E-06

Note: Results are expressed as percentage and frequency for categorical variables, mean ± SD for continuous variables, and median and IQR for non-normally distributed continuous variables. Statistical significance of differences between groups was calculated according to normality and homoscedasticity assumptions: when those were met, a parametric test, i.e., *t* test was used (1); otherwise, nonparametrical Wilcoxon rank sum test was applied (2). For categorical variables, Pearson χ^2 test with Yates continuity correction was used (3).

Abbreviations: CRP, C-reactive protein; DBP, diastolic blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; PHQ9, Patient Health Questionnaire 9 items; SBP, systolic blood pressure; WBC, white blood cells.

[a]Former smoker >1 year; current smoker at least 1 cigarette/day during the last 6 months.

TABLE 2 Brain regions showing increased fractional perfusion in the participants with obesity ($n = 72$) compared with those without obesity ($n = 66$).

Cluster	Brain region	MNI peak coordinates (x, y, z)	K_E	Size p_{FDR}	Peak p_{uncorr}
Cluster 1	Middle frontal gyrus Inferior frontal gyrus-operculum Pre- and postcentral gyrus Superior temporal cortex Posterior cingulate	26, 50, 12 34, 36, 0 52, −20, 28 52, −4, −6 −4, −40, 28	2667	0.000000	0.000000
Cluster 2	Subgenual cingulate cortex	−6, 22, −14	137	0.010006	0.000007
Cluster 3	Midbrain	16, −18, −16	501	0.000002	0.000000
Cluster 4	Ventral caudate Putamen	12, 4, 2 30, −10, 12	280	0.000206	0.000000
Cluster 5	Right orbitofrontal cortex	18, 12, −20	183	0.002885	0.000002
Cluster 6	Left orbitofrontal cortex	−18, 12, −18	100	0.030603	0.000000
Cluster 7	Ventromedial frontal cortex	−8, 56, −2	99	0.030603	0.000097
Cluster 8	Frontal pole	28, 48, 14	98	0.030603	0.000032

Note: Anatomical coordinates (x, y, z) are given in Montreal Neurological Institute (MNI) Atlas space. Results surpassed a voxel threshold of $p < 0.001$ uncorrected and cluster-level threshold of $p < 0.05$ (FDR-corrected).
Abbreviations: K_E, cluster extension; FDR, false discovery rate.

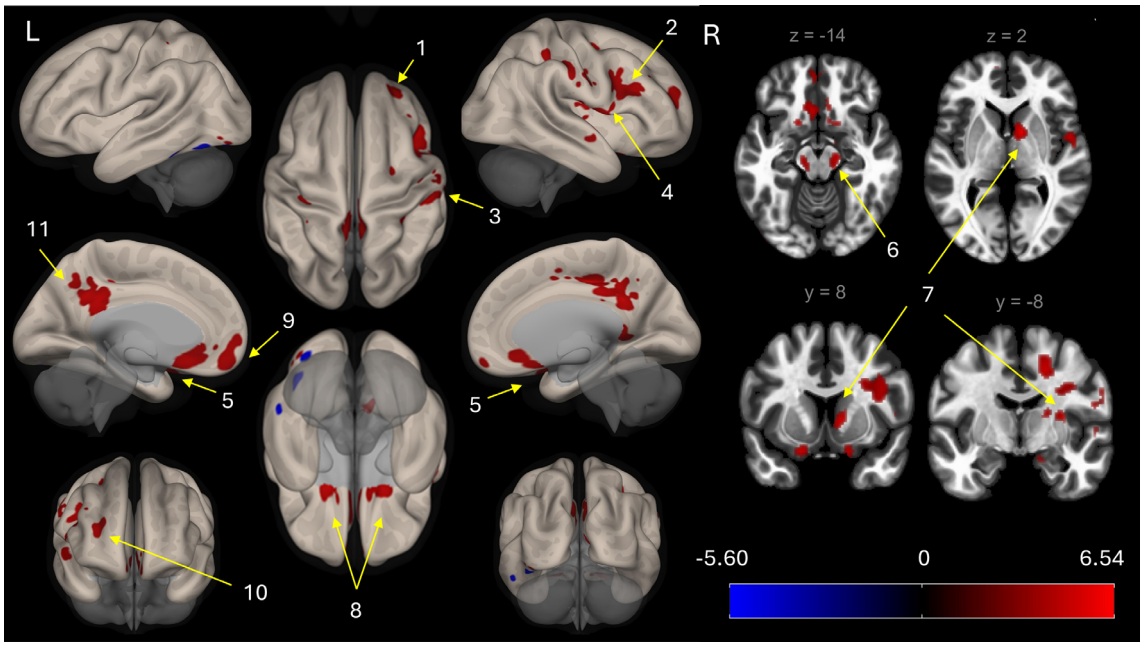

FIGURE 1 Brain regions showing higher fractional perfusion in participants with obesity compared with those without obesity. Analyses are adjusted for age, sex, education years, and alcohol intake. The right hemisphere corresponds to the right side of the axial and coronal brain views. The side of the sagittal views is indicated as L = Left, R = Right. Numbers refer to the following brain regions: 1 = Middle frontal gyrus, 2 = Inferior frontal gyrus/operculum, 3 = Pre- and postcentral gyri, 4 = Superior temporal cortex, 5 = Subgenual cingulate cortex, 6 = Midbrain, 7 = Ventral caudate/putamen, 8 = Orbitofrontal cortex, 9 = Ventromedial frontal cortex, 10 = Frontal pole, 11 = Posterior cingulate cortex. The color bar indicates *t* values. [Color figure can be viewed at wileyonlinelibrary.com]

participants with obesity exhibited a positive association between higher FP in the inferior temporal and occipital cortices and depressive symptoms, but nonsignificant associations emerged in the HCs. In addition, the group with obesity showed a significant positive association between FP in the ventral caudate and the midbrain and the total digit test performance, which was negative in the HCs, showing a significant interaction in the direct comparison between the groups (Figure 2; Table 3). In addition, the group with obesity demonstrated a higher association between FP in the midbrain and working memory performance compared to the HCs and a positive association between hyperperfusion in the temporal and occipital cortices and depressive symptoms.

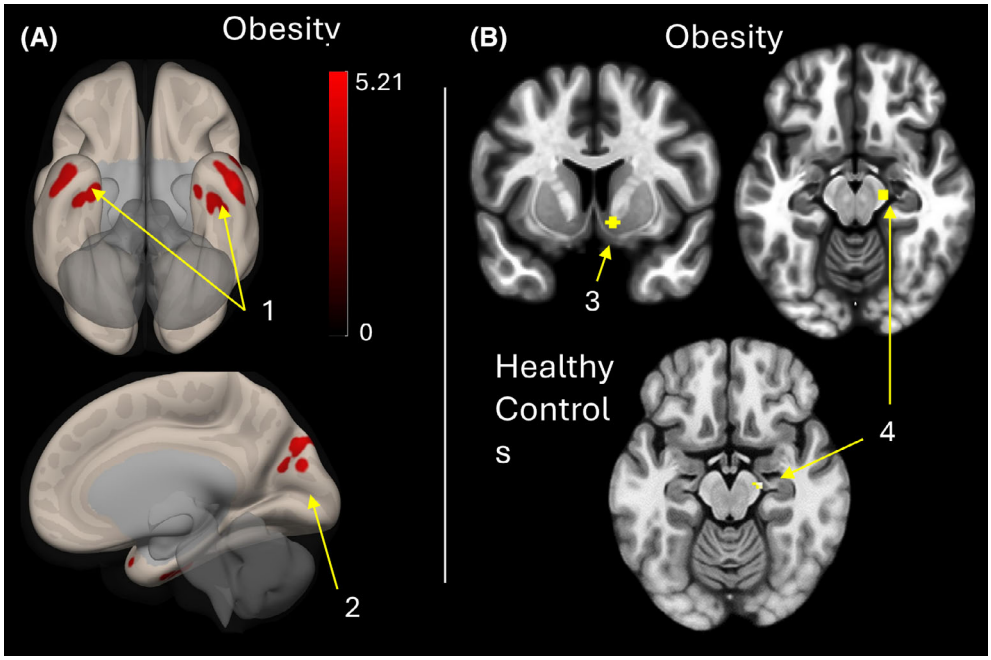

FIGURE 2 Brain regions whose fractional perfusion was significantly associated with (A) depressive symptoms and (B) total digit span scores in each of the study groups and the between-group comparisons. Analyses are adjusted for age, sex, education years, and alcohol intake. The right hemisphere corresponds to the right side of the axial and coronal brain views, and the right hemisphere is shown for the sagittal view. Numbers refer to the following brain regions: 1 = Left and right inferior temporal cortex, 2 = Occipital cortex, 3 = Ventral caudate, 4 = Midbrain. The color bar indicates *t* values. [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 3 Brain regions whose FP showed a significant association with depressive symptoms and total digit span in participants with obesity and HCs and the direct comparison between these study groups.

Brain region		MNI peak coordinates (x, y, z)	K_E	Size p_{FDR}	Peak p_{uncorr}	SVC peak p_{FWE}
Depressive symptoms						
Obesity						
Inferior temporal cortex	Left	−36, −2, −32	213	0.004	0.000	–
	Right	44, 0, −34	269	0.002	0.000	–
Occipital cortex	Right	14, −80, 36	140	0.024	0.000	–
Total digit span						
Obesity						
Ventral caudate	Right	8, 8, −6	13	–	–	0.001
Midbrain	Right	16, −18, −16	21	–	–	0.004
HCs						
Midbrain	Right	18, −16, −16	13	–	–	0.039
Obesity > HCs						
Midbrain	Right	16, −16, −14	27	–	–	0.005

Note: Anatomical coordinates (x, y, z) are given in Montreal Neurological Institute (MNI) Atlas space. Results surpassed a voxel threshold of $p < 0.001$ uncorrected and cluster-level threshold of $p < 0.05$ (FDR-corrected) or small volume correction $p_{FWE} < 0.05$ inside a 3.5-mm sphere located in the subcortical coordinates of subcortical brain regions that showed differences in FP between the groups.
Abbreviations: K_E, cluster extension; FDR, false discovery rate; FP, fractional perfusion; HC, healthy controls; SVC, small volume correction; FWE, family-wise error.

Contributing clinical variables

Inflammatory (blood monocyte cell count, serum ferritin) and metabolic variables (serum glucose, blood glycated hemoglobin, serum uric acid, and plasma alanine aminotransferase activity) were identified as the most significant predictors of FP in all participants (Figure 3). Among participants with obesity, the inflammatory (blood monocyte cell count) and metabolic variables (serum glucose, serum insulin,

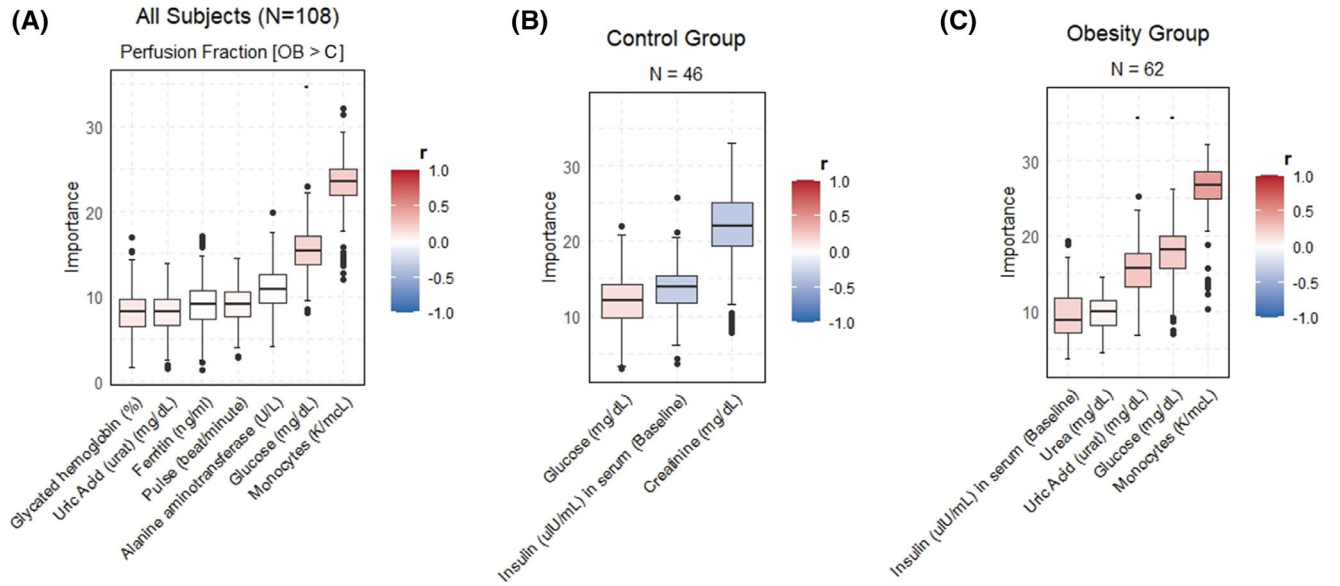

FIGURE 3 Variables associated with FP of brain regions showing a significant difference between the groups as determined using a multiple random forest-based machine learning variable selection strategy using the Boruta algorithm with 5000 trees and 1000 iterations in (A) all participants, (B) controls, and (C) participants with obesity. In box plots red and blue colors indicate variables that have a positive or a negative association with FP, respectively, as determined by Pearson correlations and multiple comparisons adjustments by FDR. FP, fractional perfusion; C, controls; OB, obesity. [Color figure can be viewed at wileyonlinelibrary.com]

serum uric acid, and serum urea concentrations) remained as positive predictors of FP. By contrast, serum glucose emerged as a positive contributor variable for FP in the HCs. Paradoxically, serum insulin and serum creatinine also contribute negatively to FP in the latter group (Table S1; Figure 3).

DISCUSSION

To the best of our knowledge, this is the first study employing IVIM to examine brain perfusion in obesity. Compared to the control group, people with obesity showed higher perfusion in brain regions that belong to the dopaminergic reward system [27] including the ventromedial and lateral sections of the PFC, subgenual and posterior sections of the cingulate cortex, the striatum, and the midbrain. In addition, the group with obesity demonstrated positive associations between hyperperfusion in the temporal and occipital cortices and depressive symptoms, as well as between hyperperfusion in the nucleus accumbens and the midbrain and working memory performance. HCs showed a negative association between working memory and perfusion in the midbrain, with this brain region showing a significant interaction in the direct comparison between the groups. Finally, contributing variables to perfusion involved inflammatory markers in obesity, with monocytes leading the way.

The increased perfusion in the dopaminergic brain reward system in participants with obesity is congruent with previous reports of functional and metabolic alterations in this brain network in obesity [27, 28]. However, most previous studies assessing cerebral perfusion in people with obesity have reported a pattern of whole [4, 5] or regional [4, 6] hypoperfusion, with isolated findings of both increases and decreases [6], or no effects [7]. Direct comparisons across our and previous findings are challenging because of differences in the characteristics of the study sample, e.g., only females in [6, 7], young adults in [9], psychiatric, neurologic [7], and medical comorbidities (heart failure [10]), the participant's state at the time of assessment (e.g., fasting in [7]), and the technique used (SPECT, ASL, Doppler ultrasonography). For instance, the comorbidity with metabolic illness may explain the hypoperfusion pattern in previous studies [7]. In support, Rusinek and colleagues [7] showed that individuals with insulin resistance showed a reduced cerebral blood flow compared to a control group of metabolically healthy individuals ranging from lean to obesity. In a similar line, Silvah et al. [6] reported both increased and decreased regional cerebral perfusion in female participants free of metabolic pathology, even subclinical. It is well known that a significant percentage of the participants with obesity also have a prediabetes state, which may possibly explain the pattern of increased cerebral perfusion. If we focus on the few studies that have used IVIM techniques, Bergamino et al. [16, 17] reported a gradient of increased cerebral perfusion from mild cognitive impairment (MCI) to AD patients and suggested the pattern of hyperperfusion in individuals with MCI as an early biomarker for neurodegenerative processes, possibly reflecting increased fast water diffusion related to cell death. In addition, several studies showed hyperperfusion in brain regions vulnerable to AD pathology in young high-risk individuals [29–31], which was attributed to early capillary dysfunction, decreased oxygen extraction by microvasculature tissue, and a compensatory increase in cerebral blood flow [32, 33]. Interestingly, a relationship between cerebral blood flow and the dopaminergic system has been described,

in which penetrating arterioles and capillaries are in contact with dopaminergic fibers in the frontal lobe, and dopamine in low concentrations acts as a vasodilator [34]. In fact, peripheral and central dopamine systems are sensitive to environmental stress, such as a high-fat diet [35]. The interaction between central dopaminergic neurotransmission and cerebrovascular function may determine brain perfusion in obesity conditions.

Associations with cognition and depressive symptoms

The association between working memory performance and the hyperperfusion pattern in the ventral caudate and the midbrain could indicate a compensatory mechanism in the participants with obesity, who had lower working memory than the control group. This association is congruent with a study showing that improved executive function is associated with hyperperfusion in younger 4 APOE genotype gene carriers, suggesting that compensatory mechanisms may have been activated years before the onset of symptoms [36]. Notably, although working memory involves the activation and functional interaction of the midbrain, caudate, and dorsolateral PFC, as well as the corticostriatal dopaminergic network [37], better performance in the group with obesity does not involve the prefrontal regions. Depressive symptoms, which were increased in this group in accordance with the high comorbidity between these conditions [38], were in turn positively associated with higher perfusion in the inferior temporal and occipital cortices in the group with obesity. Fountoulakis et al. [39] found different patterns of brain perfusion depending on the type of depression. SPECT studies [40, 41] also showed increased cerebral blood flow in occipital areas in patients with major depression disorder and suggested that cognitive dysfunction in depressed patients could originate from aberrant occipital lobe activity. Depression is also associated with atrophy of the structures of the medial temporal lobe [41] and has been related as an early indicator of MCI or AD [42].

Associations with metabolic traits

Numerous clinical biochemical inflammatory and metabolic markers, such as blood monocytes, serum glucose, serum insulin, uric acid, and urea, were found to be positively correlated with brain perfusion in individuals with obesity. We found that the variable that was most positively associated with cerebral perfusion in obesity was blood monocyte count. Prior research demonstrated a significant increase in monocytes in individuals with obesity [43]. Monocytes are diverse blood cells that play a key function in the innate immune response to inflammation. According to Arce-Sillas et al. [44] and Levite [45], intermediate monocytes, among others, express dopamine receptors, and peripheral monocytes' high-affinity dopamine receptor stimulation appears to promote these cells' production of several inflammatory cytokines [45]. In addition, we also found that serum insulin was positively associated with brain hyperperfusion in individuals with obesity but surprisingly had the opposite effect in HCs. Insulin affects many aspects of human physiology, including the central control of energy homeostasis, cognition, and neuronal activity [46]. The inverse associations of insulin with brain perfusion might represent physiological effects in the context of normal plasma insulin levels in individuals without obesity. In contrast, in those with obesity, with a range of plasma insulin that is threefold higher compared with those without obesity, concomitant inflammation associated with increased fatness could contribute to the positive associations observed, as other research has appointed [47]. Plasma glucose has a positive association with cerebral perfusion in both groups. In this line Ikeda et al. [48] found that central dopamine D_2 receptors regulated plasma glucose via parasympathetic nerves in a mice model, suggesting that stimulation of central dopamine D_2 receptors increases plasma glucose levels. Additionally, uric acid appeared to be relevant for cerebral perfusion in obesity. Moccia et al. [49] proposed for the first time a correlation between dopaminergic impairment (in the caudate, putamen, and striatum) and serum uric acid levels in early Parkinson disease. This suggested that uric acid may serve as a biomarker for Parkinson disease, and we speculate that this could also be applicable to our findings in obesity. Finally, plasma urea has been related to cerebral blood flow and identified as a biomarker of the vascular brain that can predict brain ischemia [50].

Conclusions

In conclusion, the findings support a differential perfusion in brain regions associated with the dopaminergic system, which may be suggestive of an early microvasculature alteration or an early cognitive adaptation. The identified increases in brain FP in obesity associate with better working memory performance but higher presence of depressive symptoms. As shown in MCI and AD patients [16, 17, 36, 51], longitudinal investigations are needed to determine how FP changes in obesity-related cognitive decline. In addition, future studies may help identify the key lifestyle (e.g., high-fat and high-sugar diets, sedentary behavior) [52] and/or metabolic variables (e.g., adipose tissue, insulin resistance) associated with the increased monocyte levels [53] in obesity, which we found to significantly impact on the hyperperfusion brain pattern in these individuals.

Limitations

A few limitations should be considered and resolved in future research. First, the sample size is too small to detect higher-order correlations. When interpreting results of analyses carried out in certain subgroups, it is necessary to bear in mind the potential lack of statistical power due to small sample sizes. Also, although we adjusted for a range of potential confounders, residual confounding cannot be totally ruled out. Direct comparison with a group of individuals with obesity and metabolic disorders is needed to confirm our suggestion

that brain FP increases only in healthy nonmetabolic individuals with obesity. In addition, our study cannot provide conclusive evidence of the mechanisms underlying the hyperperfusion pattern found in the dopaminergic brain system of the participants with obesity. Analyzing the non-gaussian diffusion behavior of water (kurtosis or biexponential model) can potentially provide information on microcirculation and tissue microstructure [54], but our diffusion images were acquired with maximum *b* value of 1000 s/mm^2, limiting our ability to go deeper in the analysis of non-gaussian water movement due to cellular membrane boundaries [53, 55].

AUTHOR CONTRIBUTIONS

Anna Motger-Albertí, María Arnoriaga-Rodríguez, Mònica Giménez, and Oren Contreras-Rodríguez researched the data and wrote the manuscript. Elena de la Calle, Mònica Giménez, and Clàudia Coll-Martínez performed the statistical analysis and wrote the methodology of the manuscript. Oren Contreras-Rodríguez, Mònica Giménez, Carles Biarnés, Josep Puig, and Gerard Blasco researched the MRI data and supervised the manuscript. Oren Contreras-Rodríguez, Josep Puig, and José Manuel Fernández-Real carried out the conception and coordination of the study. All authors participated in final approval of the version to be published. José Manuel Fernández-Real and Oren Contreras-Rodríguez are 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.

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CONFLICT OF INTEREST STATEMENT

The authors declared no conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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