Online Appendix, Supplementary Material

Neuroimaging post-processing and software

FDG-PET

The cardiac PET scan was reconstructed into 26 frames of increasing durations (1x10, 8x5, 4x10, 2x15, 3x20, 4x30, 6x60 s). The brain PET scan was reconstructed into frames of 5 min duration each. All images were reconstructed using time-of-flight ordered subsets expectation maximization using 2 iterations and 28 subsets, including resolution recovery, and a 5 mm gaussian post-filter. A 1 cm diameter volume of interest was placed over 10 slices in the ascending aorta in the frame where it was best visible and transferred to all image frames to obtain the first 10 min of the blood time-activity curve. Forward cardiac output was calculated as the ratio between the injected amount of radioactivity and the area under the curve of the first pass peak in the ascending aorta (1; 2).

PET images were corrected for inter-frame motion and whole-brain grey matter time-activity curves were extracted based on gray matter segmentation using SPM12 (Wellcome Trust Centre for Neuroimaging, London, UK). Net uptake rate of ^{18}F-FDG (K_i) and metabolic rate of glucose (MR_{glu}) during euglycemia and hypoglycemia were calculated using a dual-phase basis function implementation of an irreversible two-tissue compartment model allowing for a change in rate constants during the glucose reduction phase, both for whole brain grey matter and at the voxel level (3). Metabolic rate of glucose (MRglu) was calculated by multiplication of K_i with the plasma glucose concentration and division by 0.65, the lumped constant accounting for differences between FDG and glucose uptake in the brain. Voxel-wise differences between K_i during euglycemia and hypoglycemia and between baseline and post-RYGB were assessed using SPM12.

Arterial spin labeling (ASL)

T2-weighted Fluid attenuated inversion recovery (T2w-FLAIR) and cerebral blood flow ASL ($CBF_{ASL)}$ images were co-registered to each subject's corresponding T1-weighted image (T1w). The following grey matter (GM) regions were included in the analysis: total GM, cerebral cortical- (frontal, parietal, occipital and temporal lobe), basal ganglia- (caudate, putamen, pallidum), limbic- (amygdala and hippocampus), other subcortical regions (thalamus and hypothalamus) and cerebellar cortical regions. Grey matter (GM) tissue probability maps were segmented based on T1w images and co-registered T2w-FLAIR images. GM and white matter (WM) maps were defined with a tissue probability fraction above 75%. Cerebellum, cortical, limbic and other subcortical regions (not including hypothalamus) were segmented on 3D-T1w and co-registered T2-FLAIR images using the Freesurfer processing pipeline (version 6.0, http://surfer.nmr.mgh.harvard.edu)(4).

Hypothalamus has previously been defined in Montreal Neurological Institute (MNI)-space by Ilinsky et al (5) (data is freely available at www.humanmotorthalamus.com). The deformation field defining the transformation from subject-specific space to MNI-space was derived based on the individual T1w image and applied to all CBF_{ASL} images. Thus, hypothalamus-specific CBF values were extracted. All processing steps as described above were performed using the SPM12 toolbox (Wellcome Trust Centre for Neuroimaging, London, UK) if not stated otherwise.

fMRI: TICA analysis of functional connectivity

The following data pre-processing was applied: masking of non-brain voxels; voxel-wise de-meaning of the data; normalization of the voxel-wise variance. Pre-processed data were whitened and projected into a 20-dimensional subspace using Principal Component Analysis. The whitened observations were decomposed into sets of vectors, which describe signal

variation across the temporal domain (time-courses), the session/participant domain and across the spatial domain (maps) by optimising for non-Gaussian spatial source distributions using a fixed-point iteration technique (6). Estimated Component maps were divided by the standard deviation of the residual noise and thresholded by fitting a mixture model to the histogram of intensity values (7).

fMRI: ROI to ROI analysis

The only extension with respect to standard processing procedure was the creation of new ROIs for medial and lateral hypothalamus (MH and RH) according to Li et al (8) and the hypothalamic MRI atlas by Baroncini (8; 9): the bilateral LH (x ± 6, y − 9, z – 10 plus 2 mm sphere) and MH (x ± 4, y − 2, z − 12 plus 2 mm sphere).

Table 1: Acquisition parameters of MRI scans

Name	Sequence type	Orientation	TR/TE/TI/FA	Matrix (mm)	Slices	Other
T1W	3D-GRE	SAG	8.6/3.2/450/12	1x0.488x0.488	178	NA
T2-FLAIR	3D-TSE	SAG	7500/121/2147/90	0.6x0.488x0.488	296	NA
pCASL	3D Pseudo-Continuous FSE	TRA	4852/10.7/2025/111	1.875x1.875x4	36	PLD = 2000 LD = 1800 No flow crushing gradients
ZTE	RUFIS	TRA	0.7/0/NA/0.8	2.4x2.4x2.4	110	NA
fMRI	2D	TRA	3000/3/NA/90	3.4x3.4x3.0	45	NA

NA = Not applicable; TR = Repetition Time (ms); TE = Echo Time (ms); TI = Inversion Time (ms); FA = Flip Angle (degrees); TRA = Transversal; SAG = Sagittal; PLD = Post-Label Delay (ms); LD = Label Duration (ms); FSE = Fast Spin Echo; RUFIS = Rotating UltraFast Imaging Sequence

Statistical software

Excel (Microsoft Corporation, Redmond, WA, USA), GraphPad Prism 8 (GraphPad Software, La Jolla, CA, USA), TIBCO Statistica v 13.5.0.17 (TIBCO Software inc, Palo Alto, CA, USA) and SPSS v 27 (IBM, Armonk, NY, USA) were used for statistical analysis.

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