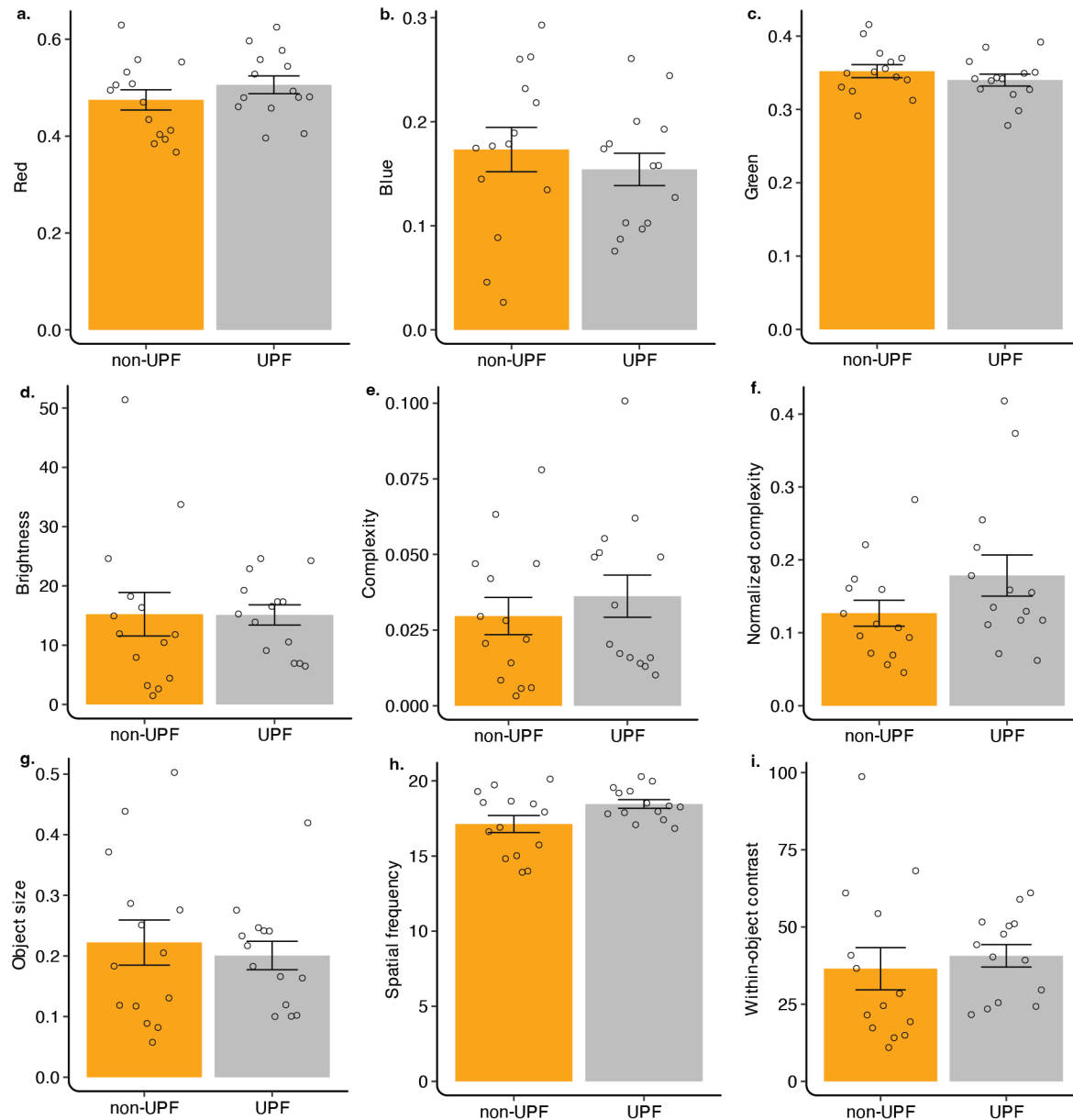
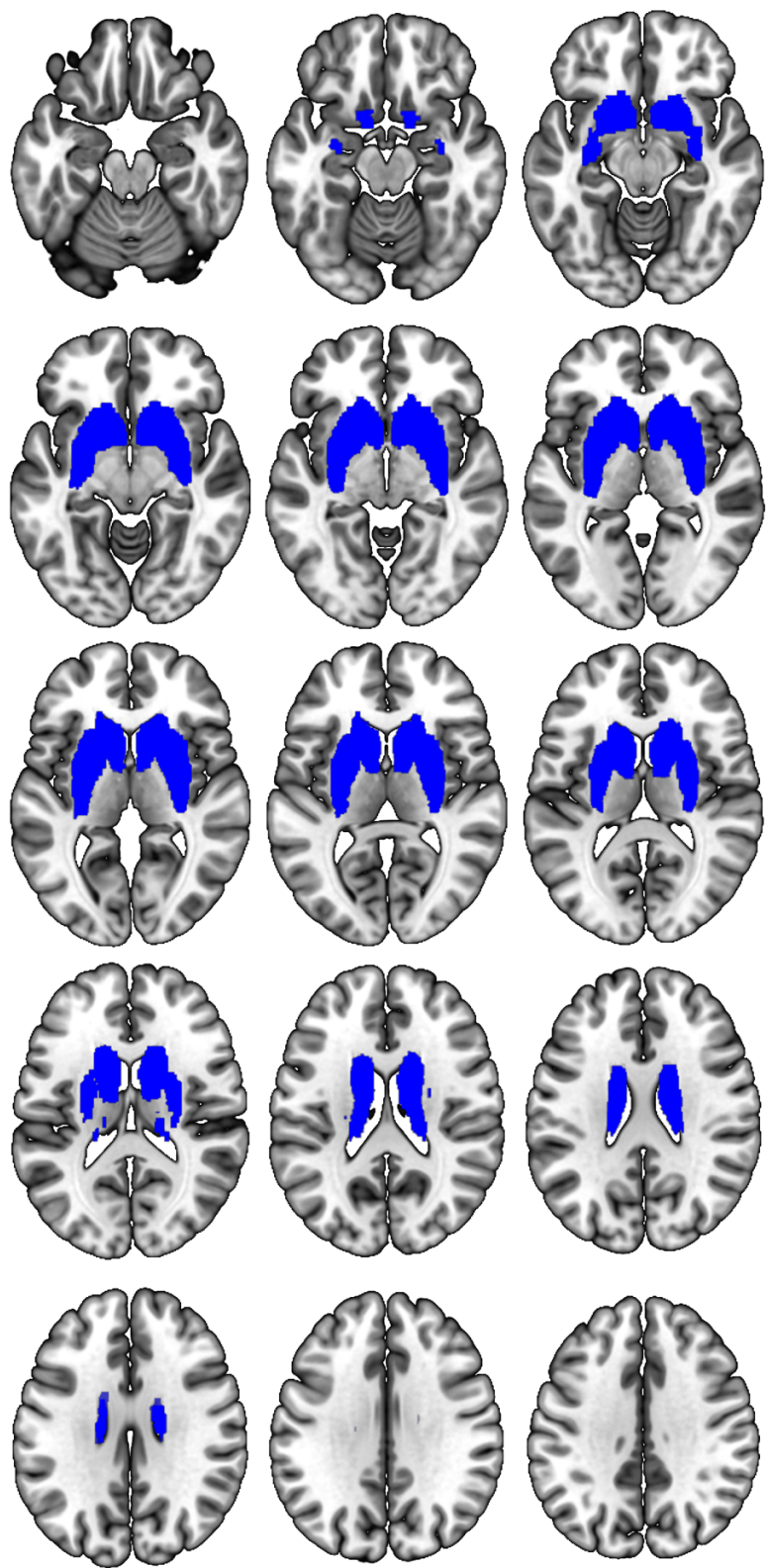


Metabolic and neural responses to ultraprocessed foods: a randomized, controlled, crossover study

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Supplemental Figure 1. Visual Properties. The non-UPF and UPF picture were sets chosen to be similar across the following visual properties: the colors a) red, b) blue, and c) green, as well as d) brightness, e) complexity, f) normalized complexity, g) object size, h) spatial frequency, and i) within-object contrast. None are statistically significantly different. UPF: ultraprocessed food, non-UPF: non-ultraprocessed food. Each dot represents a picture and error bars represent standard error of the mean.



Supplemental Figure 2. Striatal Mask. The single large mask consisted of the caudate, putamen, and nucleus accumbens derived from the Harvard–Oxford Subcortical Atlas at the most inclusive probability setting.

Food Cue Reactivity Model - Peak Carbohydrate Oxidation (non-UPF - UPF), n=29							
Whole Brain Analysis	Region	p(FWE-corr)	t	x [mm]	y [mm]	z [mm]	
non-UPF>UPF	L Superior Temporal Gyrus	0.060	6.65	-44	-24	-8	
Region of Interest Analysis	Region	p(SVC-corr)	t	x [mm]	y [mm]	z [mm]	
non-UPF>UPF	R Caudate	0.003	6.66	4	8	4	
	L Ventral Striatum	0.057	5.14	-8	6	-10	
Food Cue Reactivity Model - Peak Respiratory Exchange Ratio (non-UPF - UPF), n=29							
Whole Brain Analysis	Region	p(FWE-corr)	t	x [mm]	y [mm]	z [mm]	
non-UPF>UPF	L Superior Temporal Gyrus	0.055	6.70	-44	-24	-8	
Region of Interest Analysis	Region	p(SVC-corr)	t	x [mm]	y [mm]	z [mm]	
non-UPF>UPF	R Caudate	0.004	6.46	4	8	2	
	R Caudate	0.107	4.82	22	-12	24	
Willingness to Pay Parametric Modulation Model, n=52							
Whole Brain Analysis	Region	p(FWE-corr)	t	x [mm]	y [mm]	z [mm]	
Positive	L Orbitofrontal Cortex	0.001	6.34	-28	24	-34	
	L Orbitofrontal Cortex	0.005	5.80	-24	30	-20	
	R Cerebellum	0.002	6.06	42	-60	-40	
	R Fusiform Gyrus	0.006	5.73	46	-62	-14	
	R Lateral Occipital Cortex	0.013	5.52	44	-78	-6	
	R Bed Nucleus of the Stria Terminalis	0.005	5.76	-10	2	-4	
	L Intraparietal Sulcus	0.018	5.44	-28	-68	44	
	L Intraparietal Sulcus	0.045	5.19	-26	-60	38	
	L Posterior Cingulate Cortex	0.019	5.43	-4	-30	34	
	L Pregenual Anterior Cingulate Cortex	0.020	5.41	-14	52	4	
	L Pregenual Anterior Cingulate Cortex	0.044	5.20	-6	52	2	
	L Temporal Lobe	0.030	5.30	-58	-42	-12	
	L Putamen/Amygdala border	0.037	5.25	-32	10	-12	
Negative	L Secondary Visual Cortex	0.038	5.24	-10	-64	-4	
non-UPF>UPF	L Fusiform Gyrus	<0.0001	7.83	-32	-52	-14	
	L Lingual Gyrus	<0.0001	7.48	-24	-84	-14	
	L Lingual Gyrus	0.0001	6.74	-24	-74	-8	
Region of Interest Analysis	Region	p(SVC-corr)	t	x [mm]	y [mm]	z [mm]	
non-UPF>UPF	R Putamen	0.017	4.62	32	-4	12	
	R Caudate	0.050	4.29	14	16	4	

Supplemental Table 1. Adjusting for sex, age, and *hunger*. FWE: familywise error correction, SVC: small volume correction with familywise error correction, UPF: ultraprocessed food, non-UPF: non-ultraprocessed food.

Food Cue Reactivity Model - Peak Carbohydrate Oxidation (non-UPF - UPF), n=29							
Whole Brain Analysis	Region	p(FWE-corr)	t	x [mm]	y [mm]	z [mm]	
non-UPF>UPF	L Superior Temporal Gyrus	0.050	6.76	-44	-24	-8	
Region of Interest Analysis	Region	p(SVC-corr)	t	x [mm]	y [mm]	z [mm]	
non-UPF>UPF	R Caudate	0.004	6.45	4	8	4	
	L Ventral Striatum	0.072	5.03	-8	6	-10	
Food Cue Reactivity Model - Peak Respiratory Exchange Ratio (non-UPF - UPF), n=29							
Whole Brain Analysis	Region	p(FWE-corr)	t	x [mm]	y [mm]	z [mm]	
non-UPF>UPF	L Superior Temporal Gyrus	0.027	7.08	-44	-24	-8	
Region of Interest Analysis	Region	p(SVC-corr)	t	x [mm]	y [mm]	z [mm]	
non-UPF>UPF	R Caudate	0.003	6.70	4	8	2	
	R Caudate	0.116	4.77	22	-12	24	
Willingness to Pay Parametric Modulation Model, n=52							
Whole Brain Analysis	Region	p(FWE-corr)	t	x [mm]	y [mm]	z [mm]	
Positive	L Orbitofrontal Cortex	0.001	6.27	-28	24	-34	
	L Orbitofrontal Cortex	0.004	5.82	-24	30	-20	
	R Cerebellum	0.001	6.15	42	-62	-42	
	R Fusiform Gyrus	0.007	5.69	46	-62	-14	
	R Lateral Occipital Cortex	0.014	5.50	44	-78	-6	
	R Bed Nucleus of the Stria Terminalis	0.006	5.72	-10	2	-4	
	L Intraparietal Sulcus	0.020	5.42	-28	-68	44	
	L Intraparietal Sulcus	0.035	5.26	-26	-60	38	
	L Posterior Cingulate Cortex	0.020	5.41	-4	-30	34	
	L Pregenual Anterior Cingulate Cortex	0.022	5.39	-14	52	4	
	L Pregenual Anterior Cingulate Cortex	0.045	5.19	-6	52	2	
	L Temporal Lobe	0.032	5.29	-58	-42	-12	
	L Putamen/Amygdala border	0.041	5.22	-32	10	-12	
	L Secondary Visual Cortex	0.035	5.26	-10	-64	-4	
	L Fusiform Gyrus	<0.0001	7.85	-32	-52	-14	
Negative	L Lingual Gyrus	<0.0001	7.46	-24	-84	-14	
	L Lingual Gyrus	0.0001	6.84	-24	-74	-8	
	L Lingual Gyrus	0.0001	6.84	-24	-74	-8	
Region of Interest Analysis	Region	p(SVC-corr)	t	x [mm]	y [mm]	z [mm]	
non-UPF>UPF	R Putamen	0.020	4.58	32	-4	12	
	R Caudate	0.048	4.31	14	16	4	

Supplemental Table 2. Adjusting for sex, age, and *fullness*. FWE: familywise error correction, SVC: small volume correction with familywise error correction, UPF: ultraprocessed food, non-UPF: non-ultraprocessed food.

Food Cue Reactivity Model - Peak Carbohydrate Oxidation (non-UPF - UPF), n=29							
Whole Brain Analysis		Region	p(FWE-corr)	t	x [mm]	y [mm]	z [mm]
non-UPF>UPF	L Superior Temporal Gyrus		0.021	7.19	-44	-24	-8
Region of Interest Analysis		Region	p(SVC-corr)	t	x [mm]	y [mm]	z [mm]
non-UPF>UPF	R Caudate		0.006	6.28	4	8	4
	R Caudate		0.040	5.32	22	-12	24
	L Ventral Striatum		0.059	5.13	-8	6	-10
Food Cue Reactivity Model - Peak Respiratory Exchange Ratio (non-UPF - UPF), n=29							
Whole Brain Analysis		Region	p(FWE-corr)	t	x [mm]	y [mm]	z [mm]
non-UPF>UPF	L Superior Temporal Gyrus		0.011	7.54	-44	-24	-8
Region of Interest Analysis		Region	p(SVC-corr)	t	x [mm]	y [mm]	z [mm]
non-UPF>UPF	R Caudate		0.013	5.90	22	-12	24
	R Caudate		0.015	5.81	4	8	2
Willingness to Pay Parametric Modulation Model, n=52							
Whole Brain Analysis		Region	p(FWE-corr)	t	x [mm]	y [mm]	z [mm]
Positive	L Orbitofrontal Cortex		0.001	6.26	-28	24	-34
	L Orbitofrontal Cortex		0.004	5.85	-24	30	-20
	R Cerebellum		0.002	6.03	42	-60	-40
	R Fusiform Gyrus		0.009	5.62	46	-62	-14
	R Lateral Occipital Cortex		0.017	5.45	44	-78	-6
	R Bed Nucleus of the Stria Terminalis		0.008	5.65	-10	2	-4
	L Intraparietal Sulcus		0.010	5.60	-28	-68	44
	L Intraparietal Sulcus		0.041	5.22	-26	-60	38
	L Posterior Cingulate Cortex		0.022	5.39	-4	-30	34
	L Pregenuel Anterior Cingulate Cortex		0.025	5.35	-14	52	4
	L Pregenuel Anterior Cingulate Cortex		0.042	5.21	-6	52	2
	L Temporal Lobe		0.029	5.31	-58	-42	-12
	L Putamen/Amygdala border		0.049	5.17	-32	10	-12
	Negative	L Secondary Visual Cortex		0.050	5.17	-10	-64
non-UPF>UPF	L Fusiform Gyrus		<0.0001	7.93	-32	-52	-14
	L Lingual Gyrus		<0.0001	7.40	-22	-84	-14
	L Lingual Gyrus		0.0001	6.88	-24	-74	-8
Region of Interest Analysis		Region	p(SVC-corr)	t	x [mm]	y [mm]	z [mm]
non-UPF>UPF	R Putamen		0.015	4.65	32	-4	12
	R Caudate		0.039	4.37	14	16	4

Supplemental Table 3. Adjusting for sex, age, and *thirst*. FWE: familywise error correction, SVC: small volume correction with familywise error correction, UPF: ultraprocessed food, non-UPF: non-ultraprocessed food.

Food Cue Reactivity Model - Peak Carbohydrate Oxidation (non-UPF - UPF), n=29							
Whole Brain Analysis	Region	p(FWE-corr)	t	x [mm]	y [mm]	z [mm]	
non-UPF>UPF	L Superior Temporal Gyrus	0.019	7.25	-44	-24	-8	
Region of Interest Analysis	Region	p(SVC-corr)	t	x [mm]	y [mm]	z [mm]	
non-UPF>UPF	R Caudate	0.018	5.73	4	10	2	
	L Ventral Striatum	0.044	5.27	-8	6	-10	
Food Cue Reactivity Model - Peak Respiratory Exchange Ratio (non-UPF - UPF), n=29							
Whole Brain Analysis	Region	p(FWE-corr)	t	x [mm]	y [mm]	z [mm]	
non-UPF>UPF	L Superior Temporal Gyrus	0.012	7.47	-44	-24	-8	
Region of Interest Analysis	Region	p(SVC-corr)	t	x [mm]	y [mm]	z [mm]	
non-UPF>UPF	R Caudate	0.032	5.44	4	8	2	
	R Caudate	0.467	3.95	10	18	2	
	R Caudate	0.063	5.09	22	-12	24	
Willingness to Pay Parametric Modulation Model, n=52							
Whole Brain Analysis	Region	p(FWE-corr)	t	x [mm]	y [mm]	z [mm]	
Positive	L Orbitofrontal Cortex	0.001	6.24	-28	24	-34	
	L Orbitofrontal Cortex	0.006	5.74	-24	30	-20	
	R Cerebellum	0.002	5.99	42	-60	-40	
	R Fusiform Gyrus	0.010	5.60	46	-62	-14	
	R Lateral Occipital Cortex	0.017	5.46	44	-78	-6	
	R Bed Nucleus of the Stria Terminalis	0.007	5.71	-10	2	-4	
	L Intraparietal Sulcus	0.021	5.40	-28	-68	44	
	L Intraparietal Sulcus	0.053	5.15	-26	-60	38	
	L Posterior Cingulate Cortex	0.023	5.38	-4	-30	34	
	L Pregenual Anterior Cingulate Cortex	0.023	5.37	-14	52	4	
	L Pregenual Anterior Cingulate Cortex	0.050	5.17	-6	52	2	
	L Temporal Lobe	0.034	5.27	-58	-42	-12	
	L Putamen/Amygdala border	0.045	5.20	-32	10	-12	
Negative	L Secondary Visual Cortex	0.049	5.17	-10	-64	-4	
non-UPF>UPF	L Fusiform Gyrus	<0.0001	7.94	-32	-52	-14	
	L Lingual Gyrus	<0.0001	7.31	-22	-84	-14	
	L Lingual Gyrus	0.0001	6.67	-24	-74	-8	
Region of Interest Analysis	Region	p(SVC-corr)	t	x [mm]	y [mm]	z [mm]	
non-UPF>UPF	R Putamen	0.015	4.67	32	-4	12	
	R Caudate	0.043	4.34	14	16	4	

Supplemental Table 4. Adjusting for sex, age, and BMI. FWE: familywise error correction, SVC: small volume correction with familywise error correction, UPF: ultraprocessed food, non-UPF: non-ultraprocessed food.

Willingness to Pay Parametric Modulation Model, n=52							
Whole Brain Analysis	Region	p(FWE-corr)	t	x [mm]	y [mm]	z [mm]	
Positive	R Fusiform Gyrus	<0.001	6.54	42	-76	-6	
	R Fusiform Gyrus	0.006	5.73	40	-70	-14	
	R Fusiform Gyrus	0.016	5.47	46	-62	-14	
	L Orbitofrontal Cortex	0.002	6.06	-24	30	-20	
	L Orbitofrontal Cortex	0.016	5.47	-28	24	-34	
	L Lateral Occipital Cortex	0.004	5.86	-44	-76	-10	
	L Temporal Lobe	0.017	5.46	-58	-40	-10	
	L Superior Frontal Gyrus	0.022	5.39	-22	32	60	
	L Superior Frontal Gyrus	<0.001	6.49	-38	-72	-12	
non-UPF>UPF	L Fusiform Gyrus	<0.001	6.44	-32	-50	-14	
	L Lingual Gyrus	0.001	6.14	-22	-88	-14	
	R Occipital Lobe	0.014	5.51	14	-100	2	
	R Occipital Lobe	0.014	5.51	14	-100	2	
Region of Interest Analysis	Region	p(SVC-corr)	t	x [mm]	y [mm]	z [mm]	
non-UPF>UPF	R Putamen	0.032	4.43	32	-2	12	
	R Caudate	0.066	4.21	16	16	4	

Supplemental Table 5. WTP model adjusting for frequency of consumption, perceived healthiness, complexity, and object size. FWE: familywise error correction, SVC: small volume correction with familywise error correction, UPF: ultraprocessed food, non-UPF: non-ultraprocessed food.

	UPF mean	non-UPF mean	t	df	p
WTP (no covariates)	2.34	2.33	0.03	30.82	0.98
WTP (including frequency of consumption and healthiness)	2.83	2.62	0.96	32.41	0.34
WTP (including frequency of consumption)	2.82	2.62	0.96	32.41	0.34
WTP (including healthiness)	2.37	2.29	0.33	31.83	0.74

Supplemental Table 6. Behavioral WTP models with and without all covariates. WTP: willingness to pay, UPF: ultraprocessed food, non-UPF: non-ultraprocessed food.

Supplementary Protocols:

Missing data from Metabolic Sessions. In any cases where a participant was missing only one of the two conditions, they were participant was included in the analysis, but if a participant had missing or invalid data for both conditions, they were dropped from the analysis. To be included in blood glucose and insulin analyses, blood had to be successfully collected for at least 4 of the 8 total time points for blood draws. For insulin data, the limit of quantification (LOQ) was 3 $\mu\text{IU/mL}$ and values below the LOQ were imputed using $3/\sqrt{2}$, as previously described.¹ Then, missing blood glucose and insulin values were imputed using a Principal Components Analysis (PCA) model,² package missMDA version 1.13, which included other covariates for a more informative imputation. Covariates included session internal states, liking and wanting ratings, calorimetry AUCs and baselines, and demographics. After imputation with the PCA model, incremental AUC was estimated with the trapezoidal rule.

Habitual diet. For each participant, three 24-hour dietary recalls were performed by the same trained researcher (ZH). Dietary recalls consisted of 2 weekdays and 1 weekend day, and all three days were averaged to represent habitual diet. For participants with a number of dietary recalls other than three, a weighted average was calculated, assigning two-thirds weight to weekdays and one-third to weekend days. Recalls were performed using the multiple pass method and recorded in Nutrition Data System for Research (NDSR; version 2022; University of Minnesota, Minneapolis, MN). Physical references and food diagrams were used to assist in the determination of portion size. Habitual ultraprocessed food consumption was determined by using the Nova classification system³. A pair of trained researchers (ZH and MEB), including a registered dietitian (MEB), independently assigned each food to a Nova categorization from the NDSR output files supplemented by notes taking during the dietary recalls. Foods that could not be definitively classified were assigned a category range consistent with best practices for Nova scoring⁴.

Metabolic session. Data from the WRIC was post processed using an 8-minute centered derivative and then further smoothed using a LOESS (Locally Estimated Scatterplot Smoothing) curve, which was implemented to avoid large outliers being selected as the peak value.

The WRIC was configured with a twin-size bed and foam wedge allowing participants to rest supine at a 30-degree angle. In this configuration, the internal volume for the WRIC is 4720 L. To minimize the influence of diurnal fluctuation in gas concentration of atmospheric air, the inflow air to the WRIC is supplied by a medical air system separate from the building supply. The inflow air was regulated by a proportional-integral-derivative (PID) controller allowing for control of CO_2 concentration inside the WRIC to a constant and optimal measurement range for the analyzer. Inflow and outflow O_2 are continuously measured with a dual channel paramagnetic sensor (Siemens Oxymat6), which ensures linearity, and inflow and outflow CO_2 are continuously measured with an infrared sensor (Siemens Ultramat6). To ensure optimal operation of the whole-room indirect calorimeter (WRIC), the system was validated regularly throughout the study using controlled blender infusions of dry N_2 and CO_2 .

Gas-infusion profiles were designed to mimic both resting and postprandial conditions.⁵ Across all validation infusions conducted over the study period ($n = 20$), mean total error for VO_2 and VCO_2 was $1.72 \pm 0.63\%$ and $0.80 \pm 0.55\%$, respectively.

Behavioral session. Liking was rated with a vertical category-ratio scale ranging from “most disliked sensation imaginable” to “most liked sensation imaginable”.⁶ Frequency of consumption was rated on an ordinal scale (“<1 x/month”, “2-3 x/month”, “1-2 x/week”, “3-4 x/week”, and “5+ x/week”). All other ratings were collected on a horizontal visual analogue scales (VAS): familiarity (“Not familiar at all” to “More familiar than anything”), expected satiety (“Not filling at all” to “More filling than anything”), perceived healthiness (“Not healthy at all” to “More healthy than anything”), estimated energy density (“Not energy dense at all” to “More energy dense than anything”), and estimated calories (kcal; “0” to “450”). These rating measures were selected to align with prior work.^{7,8}

The short version of the International Physical Activity Questionnaire (IPAQ)⁹ along with the three-factor eating questionnaire (TFEQ)¹⁰ were also administered. The IPAQ estimates weekly duration (minutes/week) of walking, moderate, and vigorous exercise while also capturing sedentary behavior with time spent sitting. The TFEQ measures three dimensions of eating behavior (cognitive restraint, disinhibition, and hunger).

fMRI session. The auction task was presented with PsychoPy3 (v2023.1.0).¹¹ Each trial consisted of a jittered inter trial interval (mean 4-sec) followed by a food picture presentation period (5-sec), jittered fixation point (mean 4-sec), bid rating (5 sec maximum). Trial order, inter stimulus interval, and intertrial interval were chosen using a genetic algorithm approach to optimize fMRI design.¹² During each run, participants bid their willingness to pay between 0 and 5 USD on 28 different foods (See Behavioral Session section) presented in a randomized order. Bids were placed on a visual analog scale with labels for \$0, \$2.50, and \$5 USD, the cursor started in the middle at \$2.50 on each trial. A modified version of the participant instructions used by Plassmann et al.¹³ were implemented to inform participants of the task. Participants were instructed that they would see a series of food items and place a bid between \$0 and \$5 dollars for each item. They were also instructed that at the end of the session, if they bid higher than a randomly computer-generated price on one randomly selected food from the trial, they would obtain and could consume that selected food, but that the computer-generated price would be deducted from their session compensation. However, if they lost to the computer on that randomly selected food, they would wait in a testing room with no food for 30 minutes.

First and group-level models. Additional nuisance regressors included Friston’s 24 head motion parameters¹⁴ (6 SPM realignment parameters, 6 of their preceding values, and 12 corresponding squared terms), the mean signal extracted from the cerebrospinal fluid and white matter (along with their preceding values, and corresponding squared terms), DVARS (D referring to the temporal derivative, VARS referring to RMS variance over voxels),^{15,16} and Framewise Displacement (FD) computed with `fsl_motion_outliers`,

and a matrix of motion-outlier volumes (DVARS threshold at 75th percentile plus 1.5 times the interquartile range and/or greater than .5 mm of Framewise Displacement).

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