

## ONLINE SUPPLEMENTAL MATERIAL

### **Post-prandial increases in liver-gut hormone LEAP2 correlate with attenuated eating behaviour in adults without obesity**

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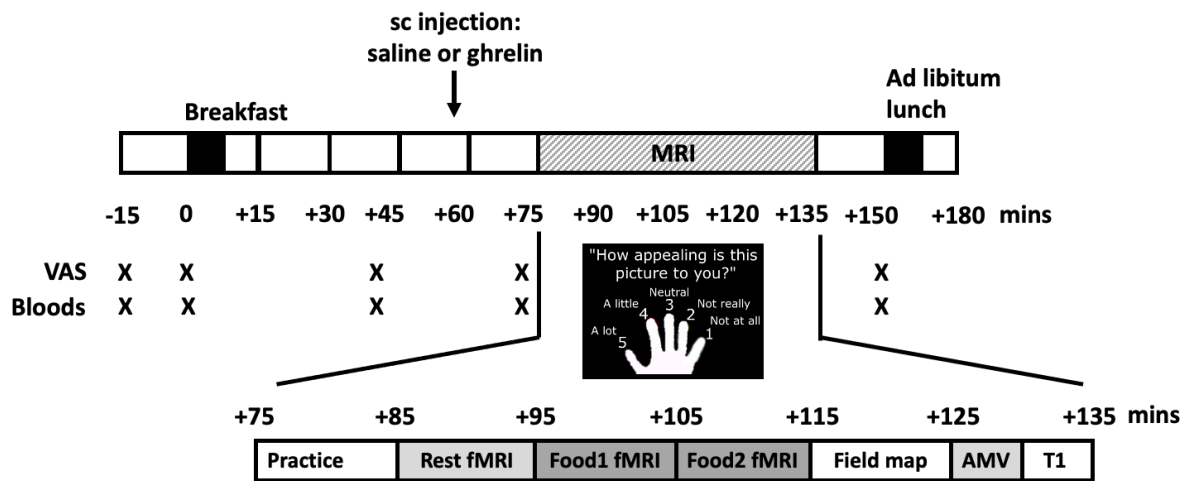
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## TABLE OF CONTENTS

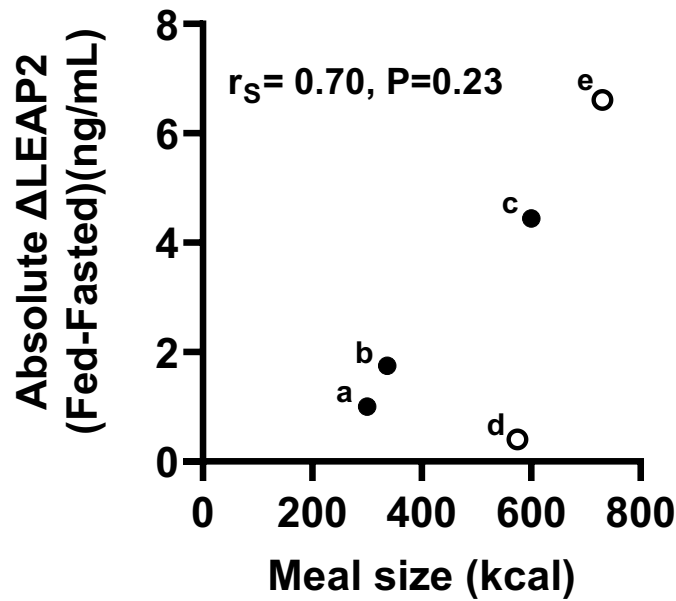
Figure S1. Study Protocol.....	3
Figure S2. Correlation of post-prandial plasma LEAP2 with meal size consumed across different studies.....	4
Figure S3. Plasma LEAP2 at study visits.....	6
Figure S4. Food appeal ratings between visits for high-energy and low-energy foods.....	7
Table S1. Whole brain analysis for correlations of post-prandial changes in BOLD signal to high-energy foods with plasma hormones.....	12
Table S2. Whole brain analysis for correlations of post-prandial changes in BOLD signal to low-energy foods with plasma hormones.....	14
Table S3. Whole brain analysis for correlations of post-prandial changes in BOLD signal to high- or low-energy foods with plasma hormones.....	16
Supplementary References .....	18

SUPPLEMENTARY FIGURES



**Figure S1. Study Protocol**

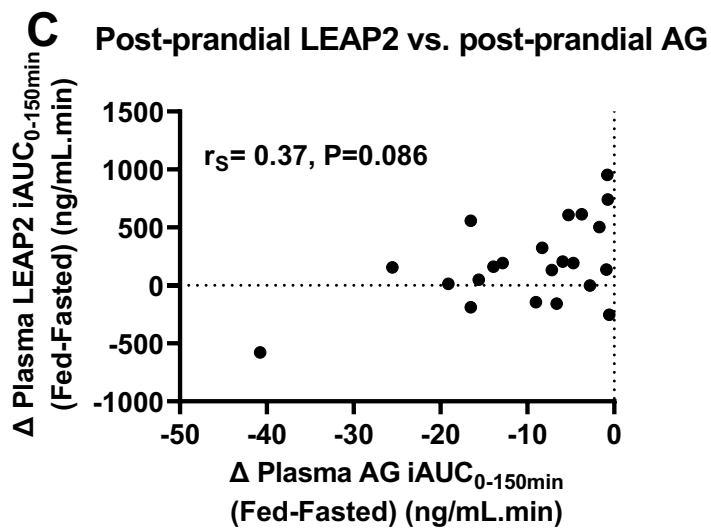
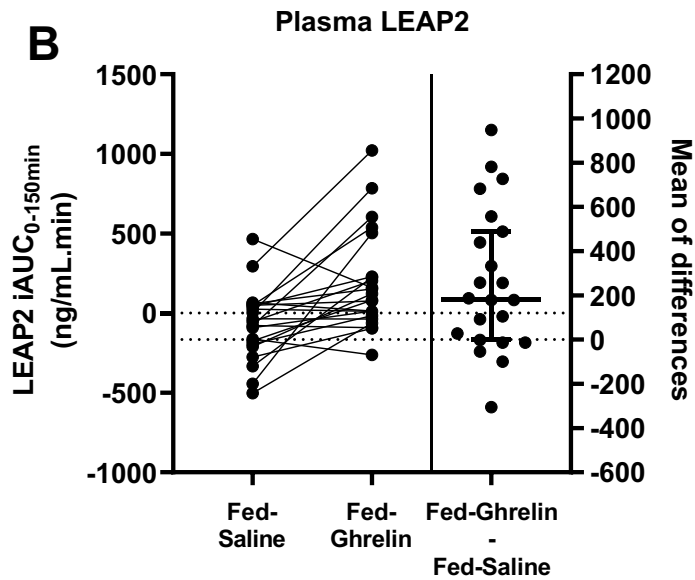
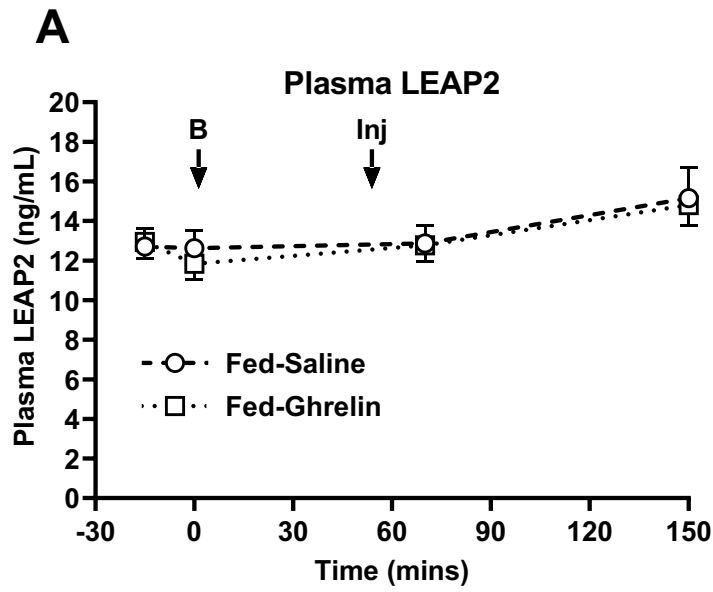
Breakfast consumption at t=+0min and saline or ghrelin injection at t=+55min. Blood and VAS measurements used for the analysis were at t= -15, 0, 40, 70 and 150 min, food picture evaluation fMRI task between t=+95 and +115min. *Ad libitum* lunch given at t=+150min. Abbreviations: AMV, auditory-motor-visual fMRI task; fMRI, functional MRI; food, food evaluation fMRI task; MRI, magnetic resonance imaging; sc, subcutaneous; T1, structural T1 MRI scan; VAS, visual analogue scales,



Study	Study	N	kcal	Macronutrient composition of meal	Post-prandial sampling (mins)
a	Hagemann et al. 2021	18	300	50% CHO, 35% fat, 15% protein	120
b	Mani et al. 2019	20	337	52% CHO, 30% fat, 18% protein	90
c	Mani et al. 2019	20	600	49% CHO, 35% fat, 16% protein	90
d	Hagemann et al. 2022	20	575	49% CHO, 35% fat, 16% protein	120
e	Current study	22	730	55% CHO, 31% fat, 14% protein	150

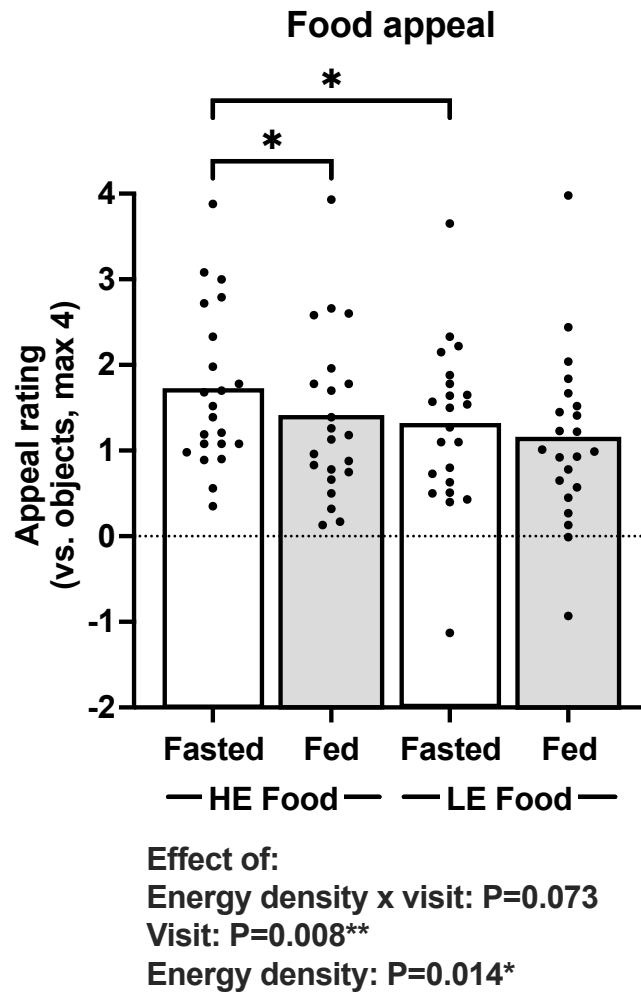
**Figure S2. Correlation of post-prandial plasma LEAP2 with meal size consumed across different studies.**

Correlation of post-prandial change in absolute plasma LEAP2 concentrations between fed and fasted time points ( $\Delta$  fed-fasted) and meal size (kcal) consumed across different studies made using Spearman's ( $r_s$ ) correlation coefficient. Black dots indicate participants with obesity (BMI  $>30\text{kg/m}^2$ ) and open dots participants without obesity (BMI  $<30\text{kg/m}^2$ ). Meals are liquid nutritional supplements with similar macronutrient composition: carbohydrates 49-55%, fat 30-35% and protein 14-18%. Table at bottom indicates details of meal and time of post-prandial blood sample for each study indicated by letters a-e: <sup>a</sup> Hagemann CA et al. J Clin Endocrinol Metab. 2021;106(2):e966-81; <sup>b,c</sup> Mani BK et al. J Clin Invest. 2019;129(9):3909-23; <sup>d</sup> Hagemann CA et al. Cell Rep Med. 2022;3(4):100582. Abbreviations: BMI, body mass index; CHO carbohydrate; kcal, kilocalorie.



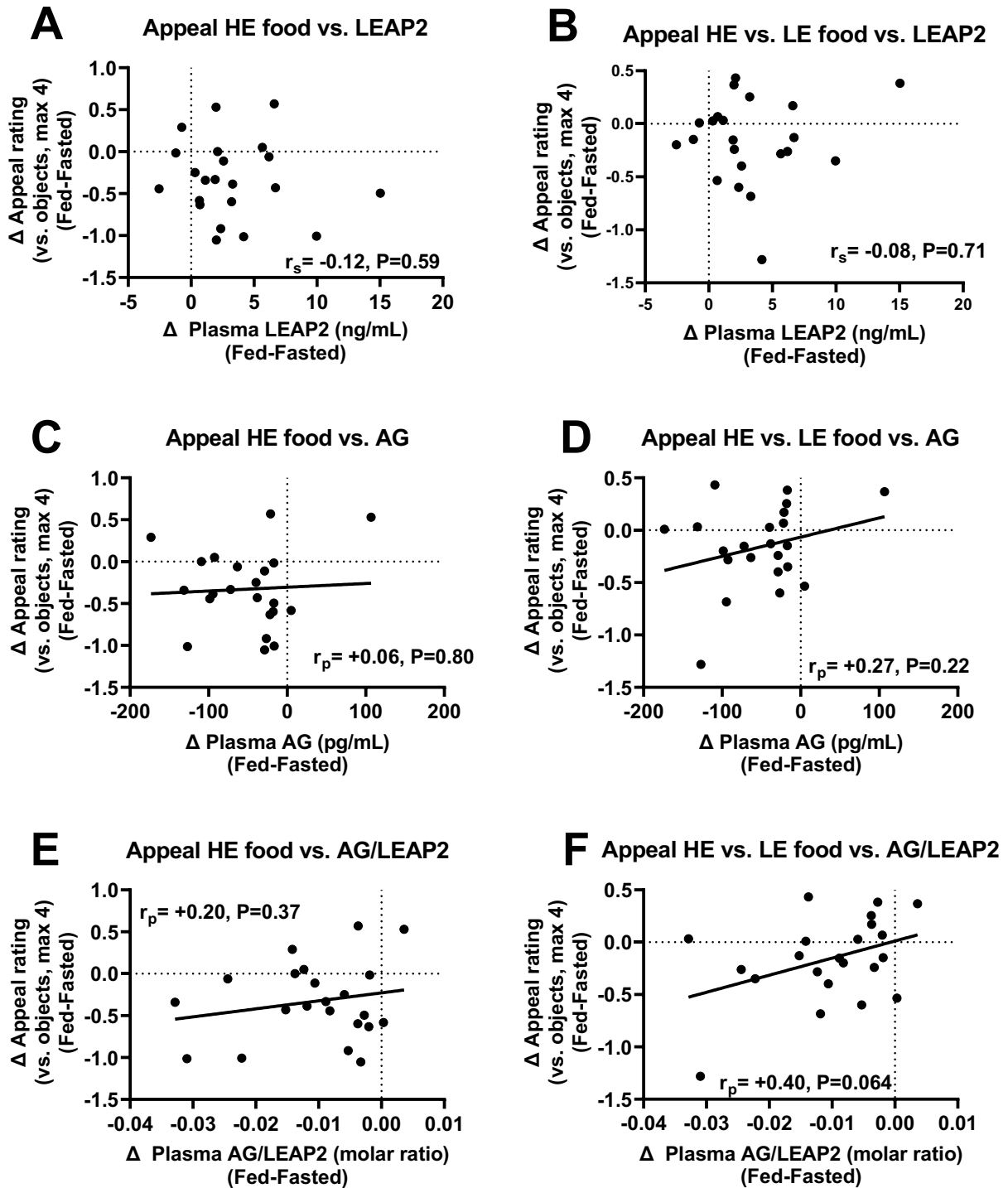
### Figure S3. Plasma LEAP2 at study visits

(A) Plasma LEAP2 concentration over study visits at Fed-ghrelin and Fed-saline visits. Arrows indicate (B) time of breakfast (t=0min) and (Inj) subcutaneous saline/AG injection (t= +55min). Comparisons made using 2-way repeated measures ANOVA with post-hoc Tukey's test: \*P<0.05, \*\*P<0.01, \*\*\*P<0.001, \*\*\*\*P<0.0001 Fed-ghrelin vs. Fed-saline, n=22. (B) Comparison of incremental value of area under the curve (iAUC) from t=0 to +150 min for plasma LEAP2 between Fed-ghrelin and Fed-saline visits with right-hand part of graph showing mean differences between visits ( $\Delta$  Fed-ghrelin minus Fed-saline). Comparisons made using Wilcoxon matched pairs signed rank test: P>0.05, n=22. (C) Correlation of change in incremental value of area under the curve (iAUC) from t=0 to +150 min between Fed-saline and Fasted-saline visits ( $\Delta$  fed-fasted) for plasma LEAP2 with change in incremental value of area under the curve (iAUC) from t=0 to +150 min between Fed-saline and Fasted-saline visits ( $\Delta$  fed-fasted) for plasma AG using Spearman's ( $r_s$ ) correlation coefficient. Abbreviations: AG, acyl ghrelin.



**Figure S4. Food appeal ratings between visits for high-energy and low-energy foods**

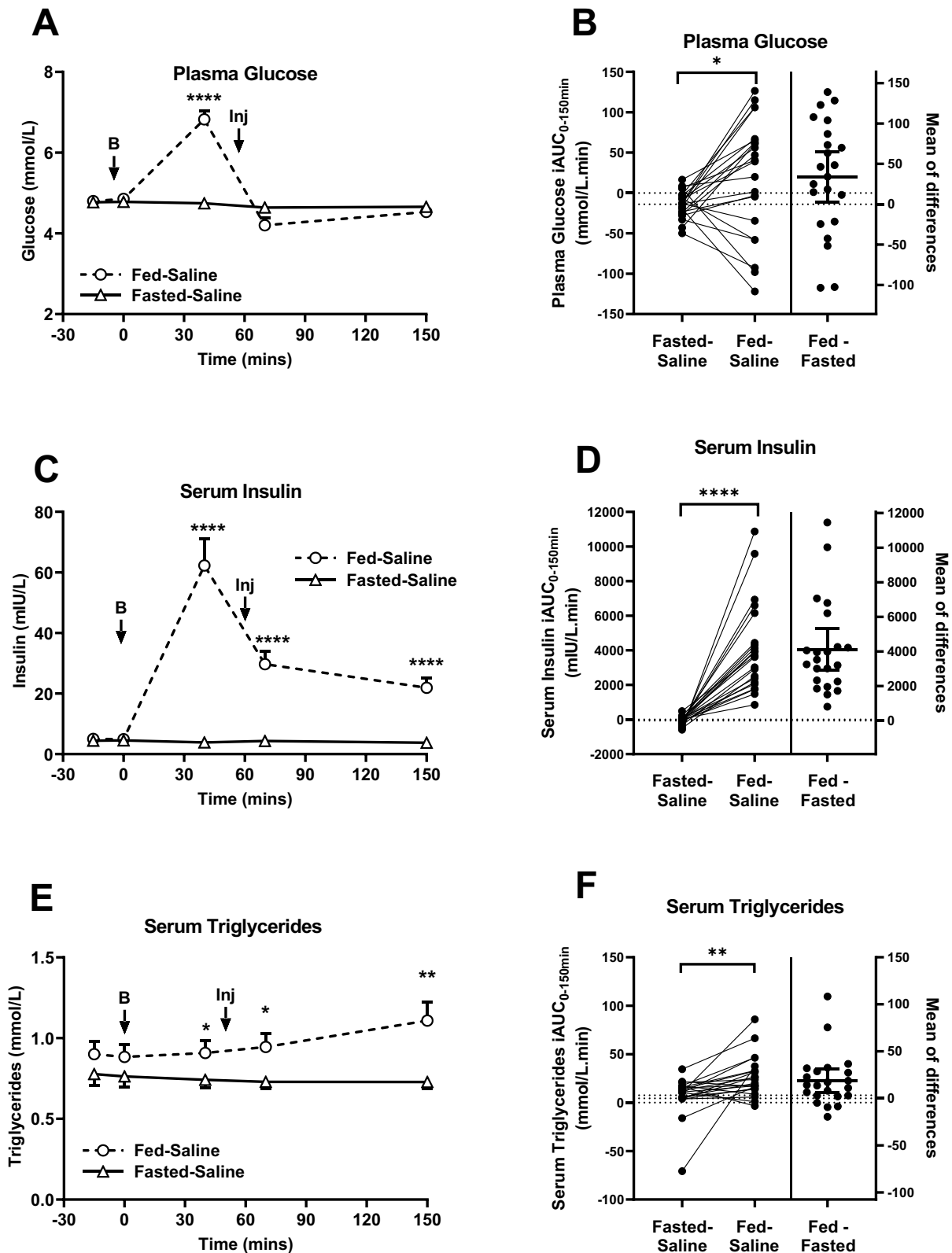
Ratings of food picture appeal (averaged at  $t=+70$  and  $+150\text{min}$ ) between Fed-saline (730 kcal breakfast, grey bars) and Fasted-saline (overnight fast, white bars) visits for high-energy and low-energy foods. Comparisons made using 2-way repeated measures ANOVA with post-hoc Tukey's test:  $*P<0.05$ ,  $**P<0.01$ ,  $n=22$ . Data given as mean (bar). Abbreviations: HE, high-energy; LE, low-energy.



**Figure S5. Correlations of post-prandial change in appeal ratings for high-energy food and high-energy vs. low-energy food with post-prandial plasma LEAP2, AG and AG/LEAP2 molar ratio**  
 Correlations of post-prandial change in appeal ratings (average of  $t = +70$  and  $+150$  min time points) between Fed-saline and Fasted-saline visits ( $\Delta$  fed-fasted) for (A,C,E) high-energy food picture appeal (vs. objects) and (B,D,F) high-energy vs. low-energy food picture appeal with change in incremental value of area under the curve (iAUC) from  $t = 0, +40, +70$  and  $+150$  min time points (except AG and



AG/LEAP2 molar ratio missing t=+40 min time point) between Fed-saline and Fasted-saline visits ( $\Delta$  fed-fasted) or plasma (A,B) LEAP2, (C,D) AG and (E,F) AG/LEAP2 molar ratio, using Pearson's ( $r_p$ , linear regression line) or Spearman's ( $r_s$ ) correlation coefficients, n=22. Abbreviations: AG, acyl ghrelin; HE, high-energy; LE, low-energy.



**Figure S6. Plasma glucose, serum insulin and triglyceride concentrations at study visits**

(A,C,E) Concentrations over study visits for (A) plasma glucose, and serum (C) insulin and (E) triglycerides at Fasted-saline and Fed-saline visits. Arrows indicate (B) time of breakfast (t=0min) and

(Inj) subcutaneous saline/acyl ghrelin injection (t= +55min). (B,D,F) Comparison of incremental value of area under the curve (iAUC) from t=0 to +150 min for (B) plasma glucose, and serum (D) insulin and (F) triglycerides between Fed-saline and Fasted-saline visits with right-hand part of graph showing mean differences between visits ( $\Delta$  fed-fasted). Comparisons made using (A,C,E) 2-way repeated measures ANOVA with post-hoc Tukey's test, (B) paired Students t-test, and (D,F) Wilcoxon matched-pairs signed rank test: \*P<0.05, \*\*P<0.01, \*\*\*P<0.001, \*\*\*\*P<0.0001 Fed-saline vs. Fasted-saline, n=22. All data given as mean  $\pm$  SEM.

**SUPPLEMENTARY TABLES**

**Table S1. Whole brain analysis for correlations of post-prandial changes in BOLD signal to high-energy foods with plasma hormones.**

Hormone	Correlation	Cluster	Number of voxels	Z	x	y	z	Laterality	Brain region
<b>LEAP2</b>	Positive	None							
	Negative	1	1462	3.70	0	24	58	B	43% superior frontal gyrus
				3.49	2	20	46	R	65% paracingulate gyrus, 5% anterior division cingulate gyrus, 5% superior frontal gyrus
				3.35	-4	-12	34	L	22% anterior division cingulate gyrus, 10% posterior division cingulate gyrus
				3.22	10	-32	38	R	31% posterior division cingulate gyrus, 5% precuneus
				3.18	2	2	46	R	44% anterior division cingulate gyrus, 27% juxta positional lobule cortex
				3.17	-2	-42	32	L	98% posterior division cingulate gyrus
		2	1445	3.55	6	34	26	R	48% paracingulate gyrus, 42% anterior division cingulate gyrus
				3.45	50	24	10	R	35% inferior frontal gyrus pars triangularis, 19% inferior frontal gyrus pars opercularis
				3.43	42	38	26	R	41% frontal pole, 24% middle frontal gyrus
				3.32	12	38	24	R	49% paracingulate gyrus, 8% anterior division cingulate gyrus
				3.29	6	48	26	R	48% paracingulate gyrus, 28% superior frontal gyrus
				3.27	20	36	24	R	99% right cerebral white matter
		3	612	3.72	4	-82	54	R	8% precuneus
				3.31	2	-62	54	R	72% precuneus
				3.19	30	-60	50	R	52% superior division lateral occipital cortex, 11% superior parietal lobule, 8% angular gyrus

				3.18	28	-64	46	R	52% superior division lateral occipital cortex
				3.11	18	-72	62	R	54% superior division lateral occipital cortex
				3.03	36	-56	58	R	35% superior division lateral occipital cortex, 25% superior parietal lobule, 5% angular gyrus
<b>AG</b>	Positive	None							
	Negative	1	403	3.59	40	-54	22	R	22% angular gyrus
				3.52	40	-68	22	R	49% superior division lateral occipital cortex
				3.49	34	-56	18	R	98% cerebral white matter
				2.88	52	-52	22	R	72% angular gyrus
				2.84	46	-52	10	R	24% temporooccipital part middle temporal gyrus
<b>AG/LEAP2 ratio</b>	Positive	None							
	Negative	None							

Group level spatial co-ordinates for correlations of post-prandial  $\Delta$  BOLD signal ( $\Delta$  fed-fasted) to high-energy foods (vs. objects) with post-prandial changes ( $\Delta$  fed-fasted) in plasma hormones (average 70/150 min) from whole-brain analysis. n=22 adults without obesity, cluster-wise family-wise error (FWE)  $Z > 2.3$ ,  $P < 0.05$ . Abbreviations: B, bilateral; L, left; R, right; Z, Z-statistic. x, y, z coordinates given in Montreal Neurological Institute (MNI) space.

**Table S2. Whole brain analysis for correlations of post-prandial changes in BOLD signal to low-energy foods with plasma hormones.**

Hormone	Correlation	Cluster	Number of voxels	Z	x	y	z	Laterality	Brain region
<b>LEAP2</b>	Positive	None							
	Negative	1	637	3.82	12	-30	80	R	32% postcentral gyrus, 16% precentral gyrus
				3.64	12	-46	76	R	35% postcentral gyrus, 21% superior parietal lobule
				3.49	-10	-34	82	L	10% postcentral gyrus, 7% precentral gyrus
				3.46	10	-42	78	R	58% postcentral gyrus, 8% superior parietal lobule
				3.36	-14	-42	78	L	57% postcentral gyrus, 7% superior parietal lobule
				3.18	-22	-22	76	L	48% precentral gyrus
<b>AG</b>	Positive	1	444	3.65	14	-90	2	R	41% occipital pole, 17% intra calcarine cortex, 9% lingual gyrus
				3.63	24	-74	-8	R	55% occipital fusiform gyrus, 10% lingual gyrus
				3.04	2	-82	-2	R	56% lingual gyrus, 25% intra calcarine cortex, 5% supra calcarine cortex
				2.93	2	-84	2	R	39% intra calcarine cortex, 26% lingual gyrus, 23% supra calcarine cortex
				2.86	26	-82	4	R	7% inferior division lateral occipital cortex
				2.86	12	-92	10	R	52% occipital pole
	Negative	None							
<b>AG/LEAP2 ratio</b>	Positive	None							

	Negative	None							
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Group level spatial co-ordinates for correlations of post-prandial  $\Delta$  BOLD signal ( $\Delta$  fed-fasted) to low-energy foods (vs. objects) with post-prandial changes ( $\Delta$  fed-fasted) in plasma hormones (average 70/150 min) from whole-brain analysis. n=22 adults without obesity, cluster-wise family-wise error (FWE)  $Z > 2.3$ ,  $P < 0.05$ . Abbreviations: L, left; R, right; Z, Z-statistic. x, y, z coordinates given Montreal Neurological Institute (MNI) space.

**Table S3. Whole brain analysis for correlations of post-prandial changes in BOLD signal to high-energy or low-energy foods with plasma hormones.**

Hormone	Correlation	Cluster	Number of voxels	Z	x	y	z	Laterality	Brain region
<b>LEAP2</b>	Positive	None							
	Negative	1	1012	3.55	18	36	24	R	99% cerebral white matter
				3.42	12	38	24	R	49% paracingulate gyrus, 8% anterior division cingulate gyrus
				3.25	32	24	26	R	12% middle frontal gyrus
				3.24	28	36	30	R	23% frontal pole, 17% middle frontal gyrus
				3.21	42	38	24	R	48% frontal pole, 16% middle frontal gyrus
				3.21	18	24	12	R	70% right cerebral white matter
		2	818	4.13	4	-82	54	R	8% precuneus
				3.66	2	-72	58	R	42% superior division lateral occipital cortex
				3.59	12	-30	80	R	32% postcentral gyrus, 16% precentral gyrus
				3.27	20	-72	62	R	48% superior division lateral occipital cortex
				3.24	8	-36	80	R	36% postcentral gyrus, 9% precentral gyrus
				3.23	10	-40	76	R	64% postcentral gyrus
		3	581	3.50	40	-32	40	R	27% anterior division supramarginal gyrus, 27% postcentral gyrus
				3.22	-2	-42	32	R	98% posterior division cingulate gyrus
				3.22	10	-32	38	R	31% posterior division cingulate gyrus, 5% precuneus
				3.17	2	-30	38	R	98% posterior division cingulate gyrus
				3.16	32	-30	46	R	19% postcentral gyrus
				3.11	28	-30	46	R	91% right cerebral white matter



<b>AG</b>	Positive	None							
	Negative	None							
<b>AG/LEAP2 ratio</b>	Positive	None							
	Negative	None							

Group level spatial co-ordinates for correlations of post-prandial  $\Delta$  BOLD signal ( $\Delta$  fed-fasted) to high- or low-energy foods (vs. objects) with post-prandial changes ( $\Delta$  fed-fasted) in plasma hormones (average 70/150 min) from whole-brain analysis. n=22 adults without obesity, cluster-wise family-wise error (FWE)  $Z > 2.3$ ,  $P < 0.05$ . Abbreviations: L, left; R, right, Z, Z-statistic. x, y, z coordinates given Montreal Neurological Institute (MNI) space.

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