Supplementary Material

Table S1: Characteristics of the *FTO* rs9939609 database subjects.						
Characteristic	***FTO* genotype**			***P* value**		
	TT (n=149)	AT (n=165)	AA (n=45)	TT *vs.* AA	AT *vs.* AA	AT *vs*. TT
Age (yrs)	22.9±0.5	23.0±0.4	23.0±0.7	*P*>0.05	*P*>0.05	*P*>0.05
BMI (kg/m^2)	22.2±0.1	22.7±0.1	22.9±0.2	*P*<0.05	*P*>0.05	*P*<0.05
Body fat (kg)	9.8±0.3	10.4±0.3	10.9±0.5	*P*<0.05	*P*>0.05	*P*>0.05
VFA (cm^2)	49.5±1.4	51.4±1.5	57.1±2.5	*P*<0.01	*P*>0.05	*P*>0.05

Values are expressed as mean ±SEM.

Table S2: Characteristics of the adiposity- matched AA and TT groups recruited for the standard test meal study.			
Characteristic	***FTO* genotype**		***P* value**
	TT (n=10)	AA (n=10)	
Age (yrs)	22.3 ± 1.2	22.8 ± 1.0	*P*=0.75
BMI (kg/m^2)	23.4 ± 0.4	23.6 ± 0.4	*P*=0.67
Body fat (kg)	11.6 ± 0.5	11.5 ± 0.7	*P*=0.95
VFA (cm^2)	58.1 ± 3.2	61.4 ± 3.3	*P*=0.49

Values are expressed as mean ± SEM.

Table S3. Composition of the standard test meal.			
Macronutrient	**Weight (g)**	**Energy (kcal)**	**Energy (%)**
Protein	50.2	201	10.9
Carbohydrate	190.2	761	41.4
Fat	97.5	878	47.7
Total	337.9	1840	

Table S4. Plasma concentrations of acyl-ghrelin, total ghrelin and acyl-ghrelin to total ghrelin ratio in standard test meal subjects.

Measurement	*FTO* genotype		*P* value
	TT (n=10)	AA (n=10)	
Fasting acyl-ghrelin (pg/l)	135 ± 15	102 ± 12	*P*=0.10
Fasting total ghrelin (pg/l)	1192 ± 195	820 ± 73	*P*=0.09
Ratio of fasting acyl-ghrelin to total ghrelin	0.13. ± 0.01	0.13. ± 0.02	*P*=0.90
AUC Δacyl-ghrelin suppression (µg/l x min)	13.0 ± 1.4	8.5 ± 1.4	*P*=0.03
AUC Δtotal ghrelin suppression (µg/l x min)	77.6 ± 17.5	46.5 ± 6.1	*P*=0.11
AUC acyl-ghrelin/total ghrelin (% x min)	1362 ± 123	1874 ± 262	*P*=0.09

Values are expressed as mean ± SEM.

Table S5. Characteristics of adiposity-matched AA and TT fMRI study subjects.			
Characteristic	***FTO* genotype**		***P* value**
	TT (n=12)	AA (n=12)	
Age (yrs)	22.1 ± 1.0	23.0 ± 0.8	*P*=0.45
BMI (kg/m^2)	21.6 ± 0.3	22.3 ± 0.5	*P*=0.26
Body fat (kg)	9.3 ± 0.6	9.8 ± 0.9	*P*=0.69
VFA (cm^2)	47.6 ± 2.5	48.8 ± 4.7	*P*=0.82

Values are expressed as mean ± SEM

Table S6. Hunger VAS and plasma acyl-ghrelin levels from fMRI subjects on their fed study day.			
	***FTO* genotype**		***P* value**
	TT (n=12)	AA (n=12)	
Fasting hunger score (mm)	82 ± 5	74 ± 5	*P*=0.26
AUC Δhunger suppression (mm x min)	10503 ± 698	7811 ± 845	*P*=0.02
Fasting acyl-ghrelin (pg/l)	201 ± 17	152 ± 14	*P*=0.04

Values are expressed as mean ± SEM.

Table S7. Effect of rs9939609 *FTO* genotype on BOLD-response to food *versus* non-food images in the fasted state.

Brain region	Laterality	Size (k)	z-score	X	Y	Z
Thalamus	L	1354	3.67	-2	-16	-6
Hippocampus	L		3.53	-10	-14	-14
VTA/SN	L		3.48	-10	-14	-12
Hypothalamus	-		3.43	-10	0	-6
Insula	L		3.07	-38	-10	-2

Brain regions in which TT subjects exhibited a greater BOLD-response to food *versus* non-food images compared to AA subjects in the fasted state. VTA: ventral tegmental area, SN: substantia nigra, $P<0.05$ family-wise error corrected for multiple comparisons on the basis of cluster extent. The X, Y, Z refer to co-ordinates in the MNI space.

Table S8. Brain regions where a significant genotype-nutritional state (TT>AA and fed>fasted) interaction was found in BOLD-response to high-calorie *versus* low-calorie images.

Brain region	Laterality	Size (k)	z-score	X	Y	Z
Insula	L	2344	4.26	-28	16	-4
Putamen	L		3.92	-26	18	-2
OFC	L		3.86	-26	24	-12

Brain regions where the TT and AA genotypes differed with respect to the state-related (i.e. Fed Vs. Fasted) modulation of neural response to high calorie, relative to low calorie, food images (i.e. a genotype-by-state interaction in the response to high-incentive food images). OFC: orbitofrontal cortex. $P<0.05$ family-wise error-corrected for multiple comparisons on the basis of cluster extent. The X, Y, Z refer to co-ordinates in the MNI space.

Table S9. Brain regions in TT and AA subjects that showed divergent correlation of BOLD-response to hedonic food images with plasma acyl-ghrelin levels in the fasted state.

Brain region	Laterality	Size (k)	z-score	X	Y	Z
Parahippocampus	L	5193	4.91	-13	-30	-16
Thalamus	L		4.68	-2	-6	-2
Superior occipital gyrus	R		4.59	24	-84	8
Parahippocampus	R		4.57	28	-26	-20
Lingual gyrus	R		4.50	20	-60	-6
Inferior OFC	L		4.29	-16	34	-6
Hypothalamus	-		4.26	8	-4	-4
Nucleus accumbens	R		3.91	6	-6	-4
Fusiform gyrus	L		3.90	-30	-38	-16
Calcarine	R		3.88	4	-54	10
Caudate nucleus	R		3.75	18	28	1
Cerebellum	R		3.71	6	-30	-14
VTA/SN	L		3.68	-6	-24	-12
SGAC	L		3.61	-8	44	-4
VTA/SN	R		3.58	8	-22	-12

Brain regions in which BOLD-response to hedonic food images positively correlated with acyl-ghrelin levels in TT subjects while negatively correlating with acyl-ghrelin levels in AA subjects. OFC: orbitofrontal cortex, VTA: ventral tegmental area, SN: substantia nigra, SGAC: subgenual anterior cingulate. $P<0.05$ family-wise error-corrected for multiple comparisons on the basis of cluster extent. The X, Y, Z refer to co-ordinates in the MNI space.

Table S10. Brain regions in TT and AA subjects that showed divergent correlation of BOLD-response to food images with post-meal acyl-ghrelin suppression.

Brain region	Laterality	Size (k)	z-score	X	Y	Z
Middle occipital gyrus	L	884	5.28	-46	-68	4
Cuneus	L	997	4.08	-12	-92	28
Precuneus	L		3.48	-20	-78	54
Middle temporal/occiptal	R	2273	3.96	34	-64	14
Precuneus	R		3.86	34	-76	36
Fusiform gyrus			3.80	46	-64	-20
Postcentral gyrus	L	1084	3.90	-52	-26	56
Inferior parietal lobe			3.51	-40	-50	64
Precentral gyrus			3.50	-60	-20	40

Brain regions in which the TT and AA groups significantly differed in their relationship between BOLD-response to food images and post-meal acyl-ghrelin suppression (t0-t54) with a positive correlation in the TT group and a negative correlation in the AA group. $P<0.05$ family-wise error-corrected for multiple comparisons on the basis of cluster extent. The X, Y, Z refer to co-ordinates in the MNI space.

Table S11. Characteristics of adiposity-matched AA and TT peripheral blood cell study subjects.			
Characteristic	***FTO* genotype**		***P* value**
	TT (n=10)	AA (n=10)	
Age (yrs)	25.0 ± 1.3	24.5 ± 1.1	*P*=0.78
BMI (kg/m^2)	23.0 ± 0.3	23.2 ± 0.5	*P*=0.75
Body fat (kg)	10.8 ± 1.0	12.6 ± 1.4	*P*=0.34
VFA (cm^2)	59.8 ± 5.8	61.8 ± 6.8	*P*=0.82

Values are expressed as mean ± SEM

Supplementary Figures

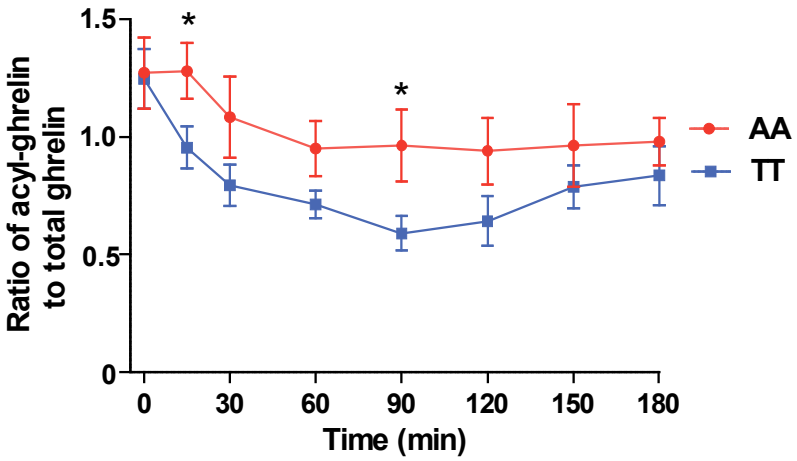

Figure S1: Plasma acyl-ghrelin/total ghrelin ratio in response to standard test meal in TT and AA subjects. Temporal profile of acyl-ghrelin/total ghrelin in response to standard test meal at t=0. Blue, filled squares represent TT subjects and red, filled circles represent AA subjects. Results are presented as mean ± SEM. * $P<0.05$.

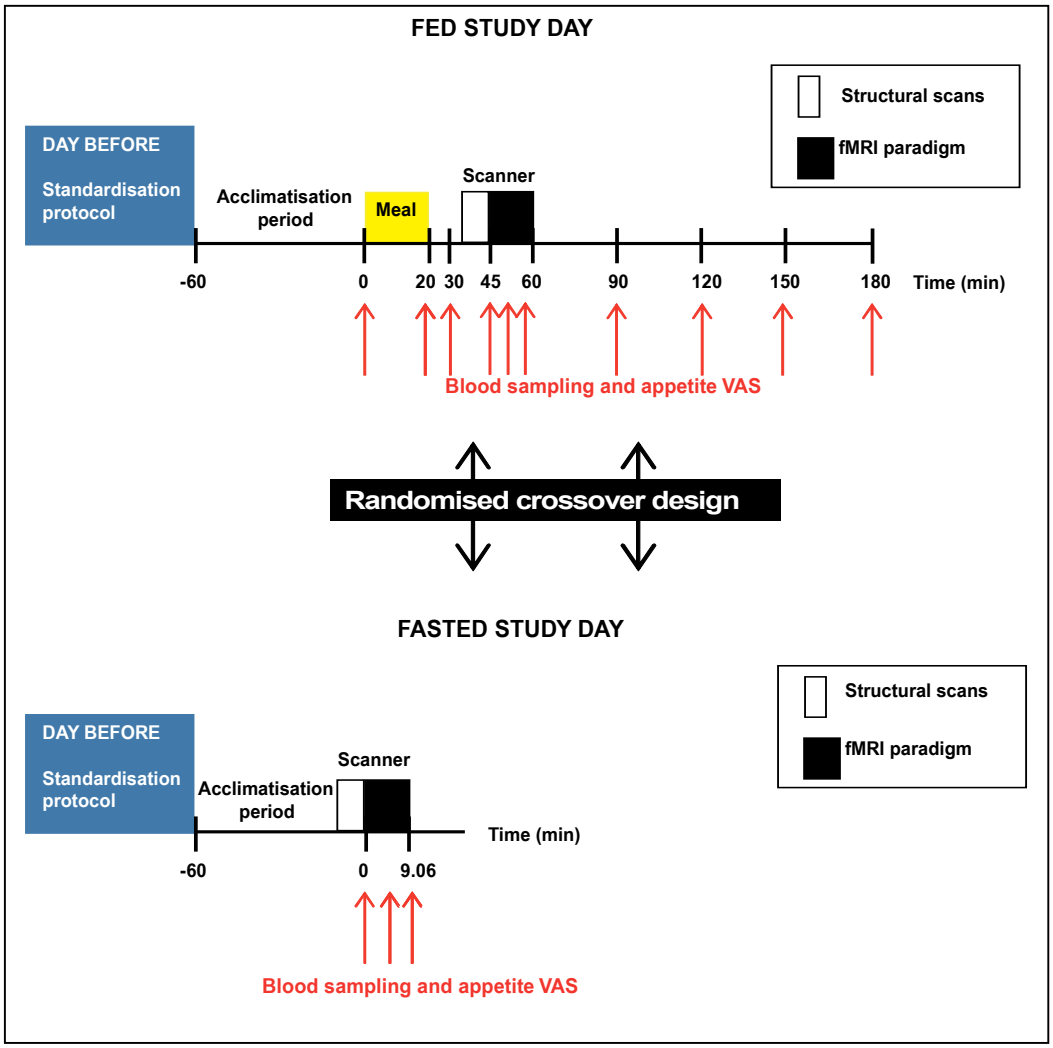

Figure S2: Randomised cross-over fMRI study protocol**.** Each subject was studied on two separate study days in the fed and fasted states in a randomised cross-over manner. On the day prior to the study, subjects abstained from alcohol and physical activity, consumed the same evening meal at 20:00 then fasted and drank only water for the 12 h prior to the study. On the study day a venous cannula was inserted into a left forearm vein and a 1 h period allowed for acclimatisation. On the fed study day at t=0 a baseline blood and appetite VAS were taken. Subjects were then given a standard test meal to consume within 20 min. Blood and appetite VAS were taken at t=20 and 30 min. At t=35 min subjects were taken into the scanner and underwent a T2-weighted scan and a fluid attenuated inversion

recovery (FLAIR) scan. At t=45 min image acquisition for BOLD scanning and the imaging task (9.06 min duration) commenced. Blood samples and appetite VAS were taken at t=45, 49.5 and 54 min within the scanner and then at t=90, 120, 150 and 180 min out of the scanner. On the fasted study day subjects were taken into the scanner at t=50 min. A high-resolution echo-planar-imaging (EPI) scan and a volumetric 3D-coronal spoiled gradient recalled echo (SPGR) scan were obtained. Image acquisition for BOLD scanning and the imaging task (9.06 min duration) commenced at t=0. Blood samples and appetite VAS were taken at t=0, 4.5 and 9 min.

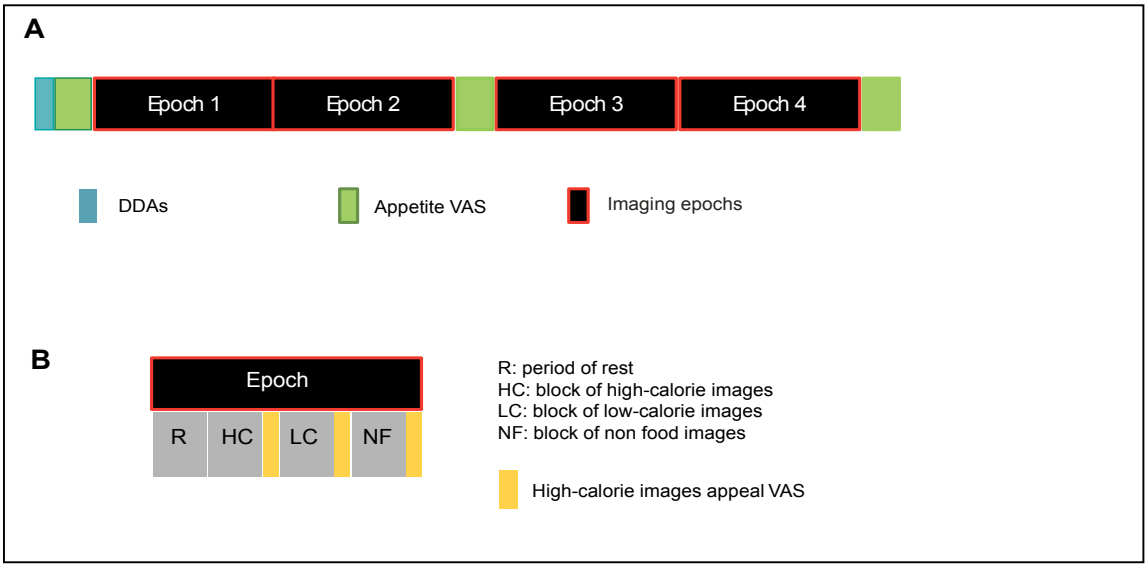

Figure S3: Schematic representation of the imaging paradigm. Each run started with four discarded dummy acquisitions (DDAs) to allow for T1 equilibration effects. There were four epochs per run. Each epoch started with a 24 s rest-period, followed by three image-viewing blocks pseudo-randomly presented in a counterbalanced way; one block consisting of high-calorie images (HC), a second of low-calorie images (LC) and a third block of non-food images (NF). Within each block eight images were presented for 3 s each, producing a block length of 24 s. At the end of each block a single VAS question *"How pleasant were the images?"* was presented. Appetite VAS were presented before the first cycle of blocks, between the second and third cycle and at the end of the task run (i.e. after the fourth cycle).