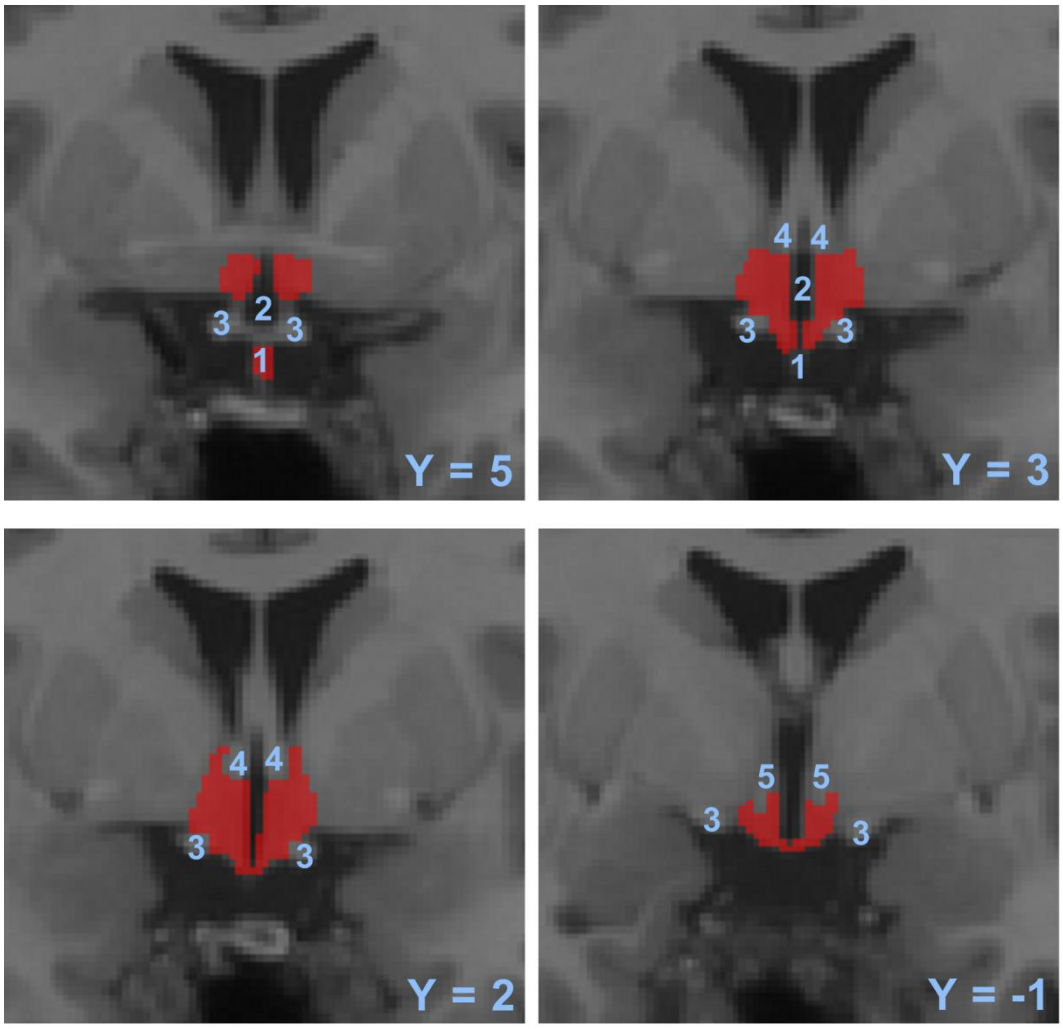
Supplementary Material

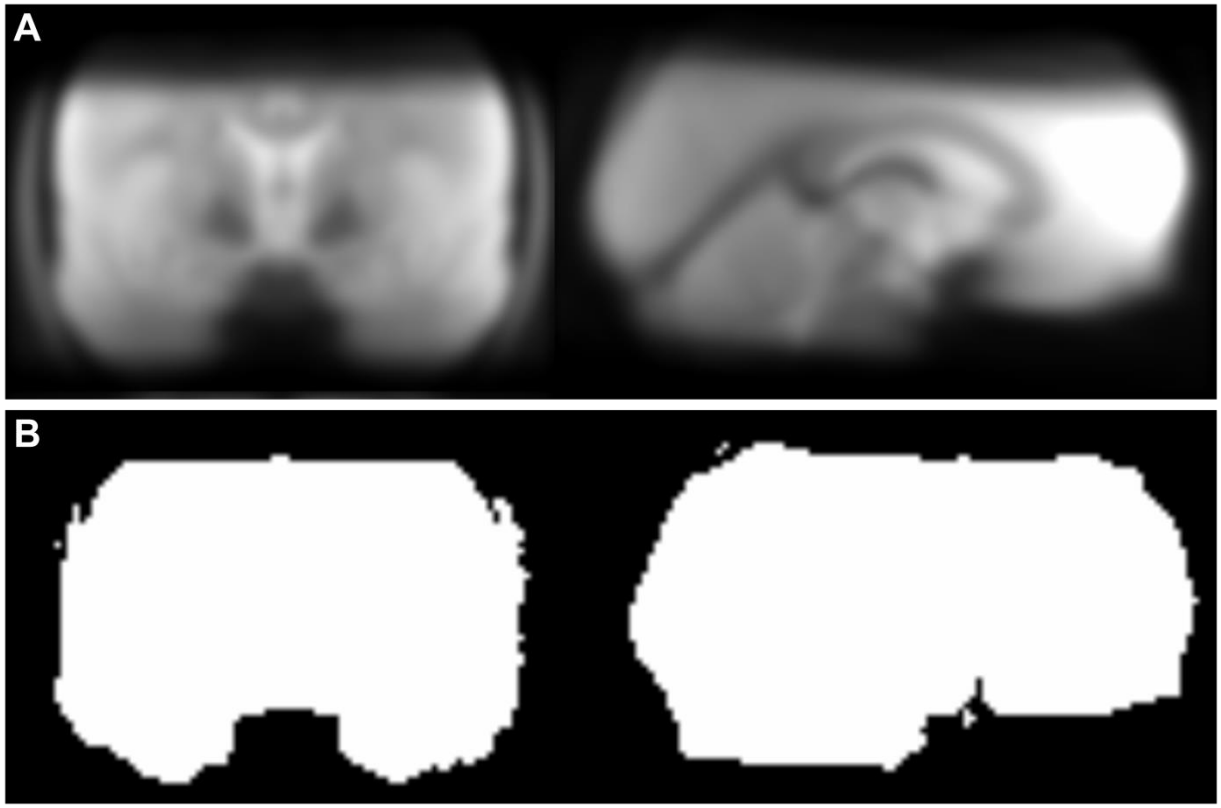
Methods

Supplementary Figure1: Manual segmentation of the hypothalamus.



Manual segmentation of the hypothalamus shown on a T1-weighted template image with annotations depicting anatomical landmarks used to identify the hypothalamic area, 1=Infundibular Stalk, 2=Third Ventricle, 3=Optic Tract, 4=Fornix, 5=Hypothalamic Sulcus.

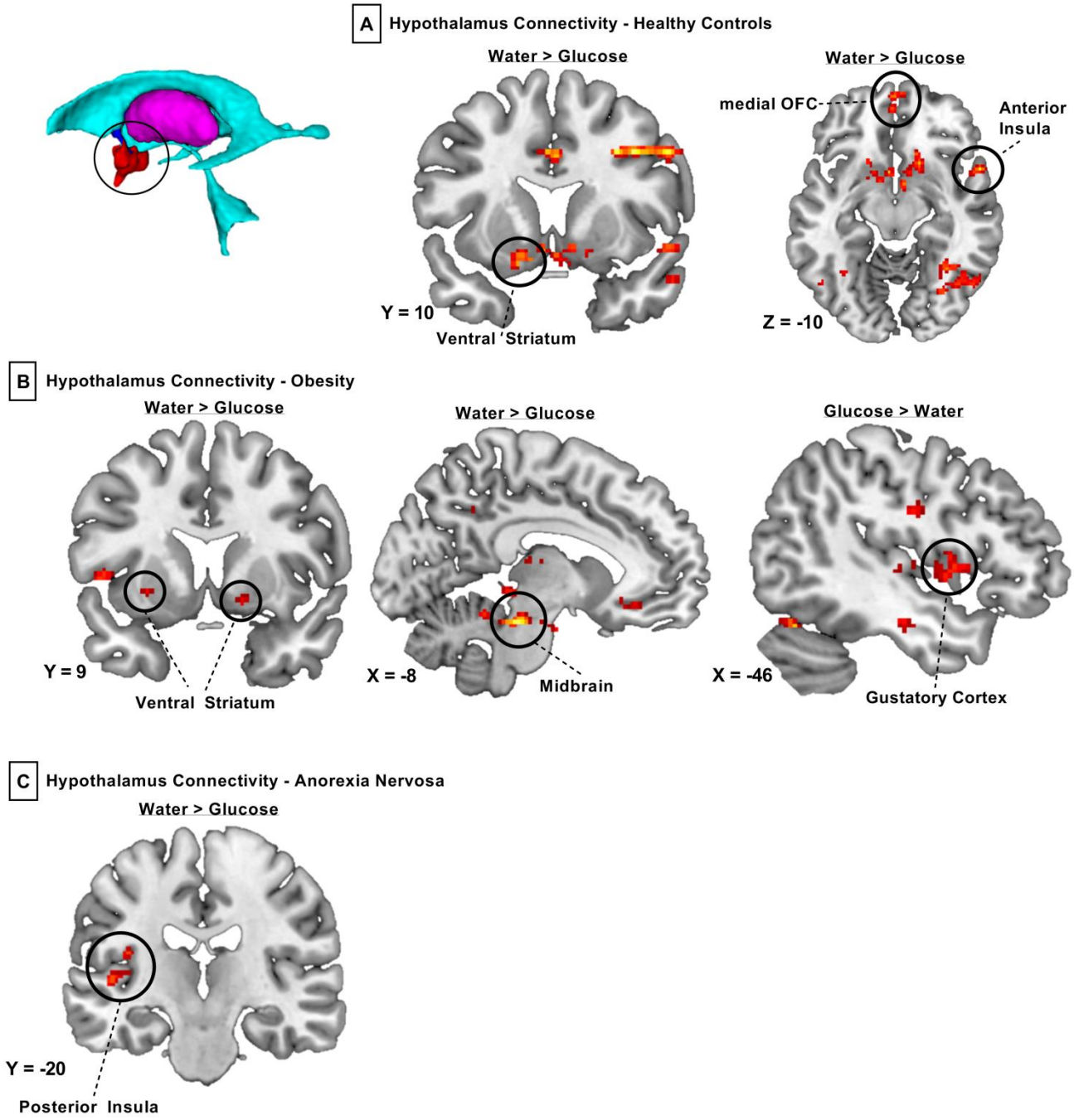
Supplementary Figure 2: Brain coverage of EPI-sequence.



A. Group-averaged functional MRI data (EPI-images) of all participants included in the study. B. 2nd-level mask used in group comparisons.

Results

Supplementary Figure 3: Satiety-state-dependent functional connectivity of the hypothalamus.



A, Satiety-state-dependent functional connectivity in healthy controls between the hypothalamus and left ventral striatum (water>glucose, mean difference: 0.136, t_{27} =

4.31, $P < 0.001$), anterior insula (water>glucose, mean difference: 0.149, $t_{27} = 4.18$, $P < 0.001$) and medial orbitofrontal cortex (water>glucose, mean difference: 0.13, $t_{27} = 4.06$, $P < 0.001$). **B**, Satiety-state-dependent functional connectivity in controls with obesity between the hypothalamus and right and left ventral striatum (right: water>glucose, mean difference: 0.144, $t_{23} = 3.57$, $P = 0.002$; left: water>glucose, mean difference: 0.138, $t_{23} = 3.73$, $P = 0.001$), midbrain (water>glucose, mean difference: 0.159, $t_{23} = 4.03$, $P = 0.001$) and gustatory cortex (glucose>water, mean difference: 0.155, $t_{23} = 4.11$, $P < 0.001$). **C**, Satiety-state-dependent functional connectivity in patients with AN between the hypothalamus and posterior insula (water>glucose, mean difference: 0.15, $t_{23} = 4.18$, $P < 0.001$).

Structural brain differences

We observed no significant differences in hypothalamic volume between normal-weight control participants and patients with AN (mean percentage of hypothalamic volume for control participants: 0.0676%, SD = 0.0052%, mean volume for patients with AN: 0.0663%, SD = 0.0069%, mean difference between groups: 0.0013%, t_{50} = 0.75, P = 0.455), but increased volume when compared to controls with obesity (mean percentage of hypothalamic volume for obese controls: 0.0639%, mean difference between groups: 0.0036%, t_{50} = 2.15, P = 0.036). Although gray and white matter volume was higher in healthy controls than in patients with AN (mean gray matter volume for control participants: 738.957 cm^3, mean gray matter for patients with AN: 664.093 cm^3, mean difference between groups: 74.863 cm^3, t_{50} = 4.676, P < 0.001, mean white matter volume for control participants: 446.929 cm^3, mean white matter for patients with AN: 412.667 cm^3, mean difference between groups: 34.259 cm^3, t_{50} = 3.765, P < 0.001), there was no significant difference in white and gray matter between healthy controls and controls with obesity (mean gray matter for participants with obesity: 727.796 cm^3, mean difference between groups: 11.16 cm^3, t_{50} = 0.647, P = 0.52, mean white matter for participants with obesity: 459.574 cm^3, mean difference between groups: -12.648 cm^3, t_{50} = -1.401, P = 0.167).

Furthermore, there was no significant difference in hypothalamic volume between patients with AN and controls with obesity (mean difference between groups: -0.0024%, t_{46} = 1.18, P = 0.242), although white and gray matter volume was significantly higher in controls with obesity than in patients with AN (mean difference in gray matter between groups: -63.702 cm^3, t_{46} = -3.104, P = 0.003, mean difference in white matter between groups: -46.907 cm^3, t_{46} = -3.941, P < 0.001).

Glucose and water induced BOLD activation in additional reward-related brain regions

Normal-weight control participants showed glucose-induced attenuation of activity in the nucleus caudatus (t_{27}=2.46, *P*=0.021), putamen (t_{27}=3.01, *P*=0.006), insular cortex (t_{27}=2.67, *P*=0.013), medial orbitofrontal cortex (t_{27}=2.93, *P*=0.007) and inferior operculum (t_{27}=2.29, *P*=0.03). Patients with AN and controls with obesity did not show a significant glucose induced deactivation in the nucleus caudatus (*P*=0.347 and *P*=0.722, respectively), putamen (*P*=0.677 and *P*=0.929), insular cortex (*P*=0.58 and *P*=0.438), medial orbitofrontal cortex (*P*=0.912 and *P*=0.587) and inferior operculum (*P*=0.827 and *P*=0.462). A group comparison revealed significant differences between all three groups in BOLD signal response in the nucleus caudatus ($F_{2,73}$=3.89, *P*=0.025): no significant differences between normal-weight control participants and patients with AN (*P*=0.065) and no significant difference between controls with obesity and patients with AN (*P*=0.345) but a stronger decrease in activation in normal-weight control participants when compared tocontrols with obesity (t_{50}=-2.65, *P*=0.011). Signal response in the putamen also proved to be different between groups ($F_{2,73}$=3.99, *P*=0.023), however, there were no significant difference between normal-weight control participants and patients with AN (*P*=0.084) but a stronger signal decrease in patients with AN as well as normal-weight control participants when compared to controls with obesity (t_{46}=-2.29, *P*=0.026 and t_{50}=-3.52, *P*=0.001, respectively). Furthermore, we observed significant differences between groups in the insular cortex ($F_{2,73}$=3.79, *P*=0.027). There were no significant differences between normal-weight control participants and patients with AN (*P*=0.132), but a stronger decrease in patients with AN and normal weight controls when compared to controls with obesity (t_{46}=-2.18, *P*=0.034 and t_{50}=-3.28, *P*=0.002, respectively). Finally, there were no groups differences in activation in the

medial orbitofrontal cortex ($F_{2,73}$=2.11, *P*=0.128) and inferior operculum ($F_{2,73}$=2.55, *P*=0.085).

Supplementary Table 1: Within group results - influence of metabolic state on hypothalamus connectivity

	Z-values	*k*	x	y	z
Healthy Controls					
Middle temporal gyrus	>8	222	56	2	-24
Pons	>8	48	16	-24	-32
Anterior insula	>8	30	56	12	-10
Ventral Striatum	7.69	229	-16	10	-16
Inferior frontal gyrus	>8	66	12	38	-24
Inferior parietal lobule	>8	71	44	-32	34
Inferior temporal gyrus	>8	97	-60	-8	-18
Temporal pole	>8	33	-36	20	-28
Hippocampus	>8	40	-36	-20	-18
Medial orbitofrontal cortex	7.39	98	0	60	-10
Patients with Anorexia Nervosa					
Cerebellum	>8	49	-10	-86	-30
Fusiform gyrus	>8	32	56	-2	-28
Middle frontal gyrus	>8	50	34	30	36
Occipital lobe	7.84	63	10	-100	8
Posterior insula	7.56	113	-38	-18	18
Middle temporal gyrus	7.52	42	68	-26	-8
Controls with obesity					
Midbrain	>8	191	-12	-26	-20
Temporal pole	>8	50	38	24	-36
Ventral striatum	>8	41	-22	-2	-2
Ventral striatum	6.95	57	24	-4	-6
Anterior Cingulate	7.61	37	2	38	8
Superior temporal gyrus	7.54	31	-56	-8	2
Gustatory cortex	7.33	85	-48	6	2
Thalamus	6.94	52	-6	-18	12
Middle temporal gyrus	6.48	33	60	-40	-8

k=Cluster size (voxels). All clusters were significant after whole-brain family-wise error correction at the cluster level $P_{FWE}<0.05$ with a minimum cluster size of $k>30$.

Supplementary Table 2: Between group results - interaction between metabolic state and group - hypothalamus connectivity

	Z-values	*k*	x	y	z
Healthy Controls vs. Patients with Anorexia Nervosa					
Middle frontal gyrus	>8	182	34	30	36
Middle temporal gyrus	>8	110	-40	8	-42
Inferior temporal gyrus	7.2	64	-58	-4	-26
Middle temporal gyrus	>8	151	56	-2	-28
Ventral Striatum	>8	151	-16	10	-14
Cuneus	>8	104	12	-100	10
Insula	>8	63	-34	-26	20
Rolandic Operculum	7.72	41	52	-24	22
Inferior parietal lobule	7.54	75	38	-36	44
Medial frontal gyrus	7.5	114	-6	48	30
Hippocampus	7.49	53	28	-34	4
Middle Occipital gyurs	7.22	31	-52	-72	4
Putamen	6.97	49	16	14	-10
Inferior orbitofrontal cortex	6.89	35	-46	40	-14
Healthy Controls vs. Controls with obesity					
Brainstem	>8	141	-6	-14	-22
Lentiform nucleus	>8	44	-18	-4	-10
Medial orbitofrontal cortex	>8	41	2	64	-2
Superior frontal gyrus	7.46	117	16	66	22
Rolandic operculum	6.89	32	56	-8	14
Superior temporal gyrus	6.69	35	-56	-8	2
Controls with obesity vs. Patients with Anorexia Nervosa					
Middle temporal gyrus	>8	178	62	-42	-10
Inferior operculum	>8	57	-48	8	4
Superior temporal gyrus	>8	165	-48	-18	2
Superior frontal gyrus	>8	108	-32	34	34
Ventral striatum	>8	48	-10	4	-6
Midbrain	>8	72	-12	-30	-6
Putamen	>8	49	-28	-8	-6
Middle frontal gyrus	7.52	71	26	50	26
Hippocampus	7.49	35	24	-32	-4
Inferior parietal lobule	7.4	49	-34	-64	40
Anterior cingulate cortex	6.66	33	-4	30	16

k=Cluster size (voxels). All clusters were significant after whole-brain family-wise error correction at the cluster level P_{FWE}<0.05 with a minimum cluster size of *k*>30.