Role of the ventral striatum in developing anorexia nervosa

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Supplementary Information

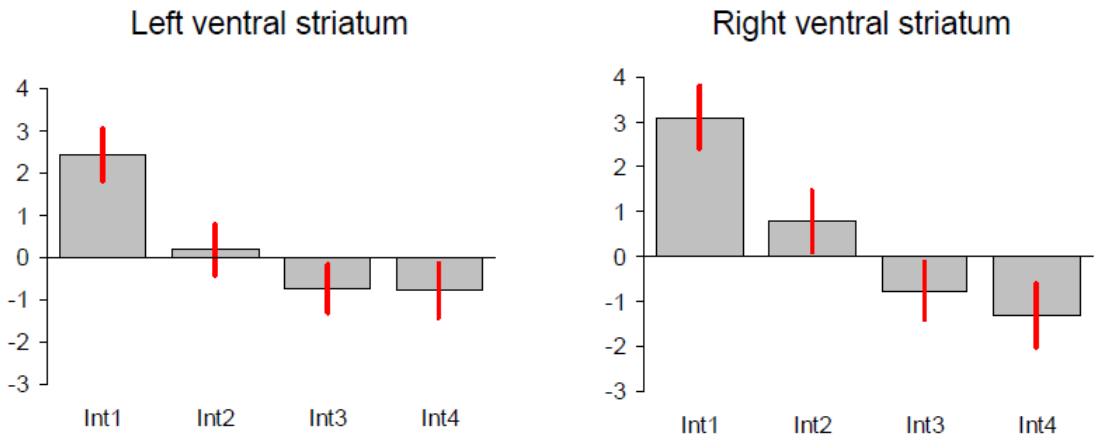
Behavioural Data

Reaction Times from subjective ratings

Although smaller in height there was also a significant interaction effect of all main factors group, task and stimulus ($F(2,50)=3.634$, $p = 0.034$) on reaction times. Bonferroni post-hoc tests (nominal level of alpha $p < 0.05$) showed that reaction times for weight-ratings did not significantly differ between groups (all p values = 1.00). In the "feel" task, however, anorexic patients' reaction times for responding on overweight stimuli were significantly faster than those of healthy comparison women ($p = 0.025$). Also within the group of patients with AN reaction times for overweight stimuli were significantly faster relative to underweight ($p < 0.0001$) and normal weight stimuli ($p < 0.001$). There were no further significant between-and within-group differences.

fMRI data

Evaluation of sizes of modelled effects in the ventral striatal ROI: Bar graphs in Figure S1 demonstrate the height of effect of the four different group-by-stimulus interactions in the left and right ventral striatum averaged over significant voxels derived from an F-contrast on these interaction effects (see Results section of the main paper). The first interaction (Int 1) tested on group differences (AN patients vs. healthy controls) contrasting neural activations on underweight against normal weight stimuli obtained under the feel task instruction. The second contrast (Int 2) tested on the same interaction for neural activations obtained under the weight task instruction. The third interaction contrast (Int 3) tested on group differences when contrasting activations on overweight against normal weight stimuli during the feel task. The fourth contrast (Int 4) tested on the same interaction during the weight task.



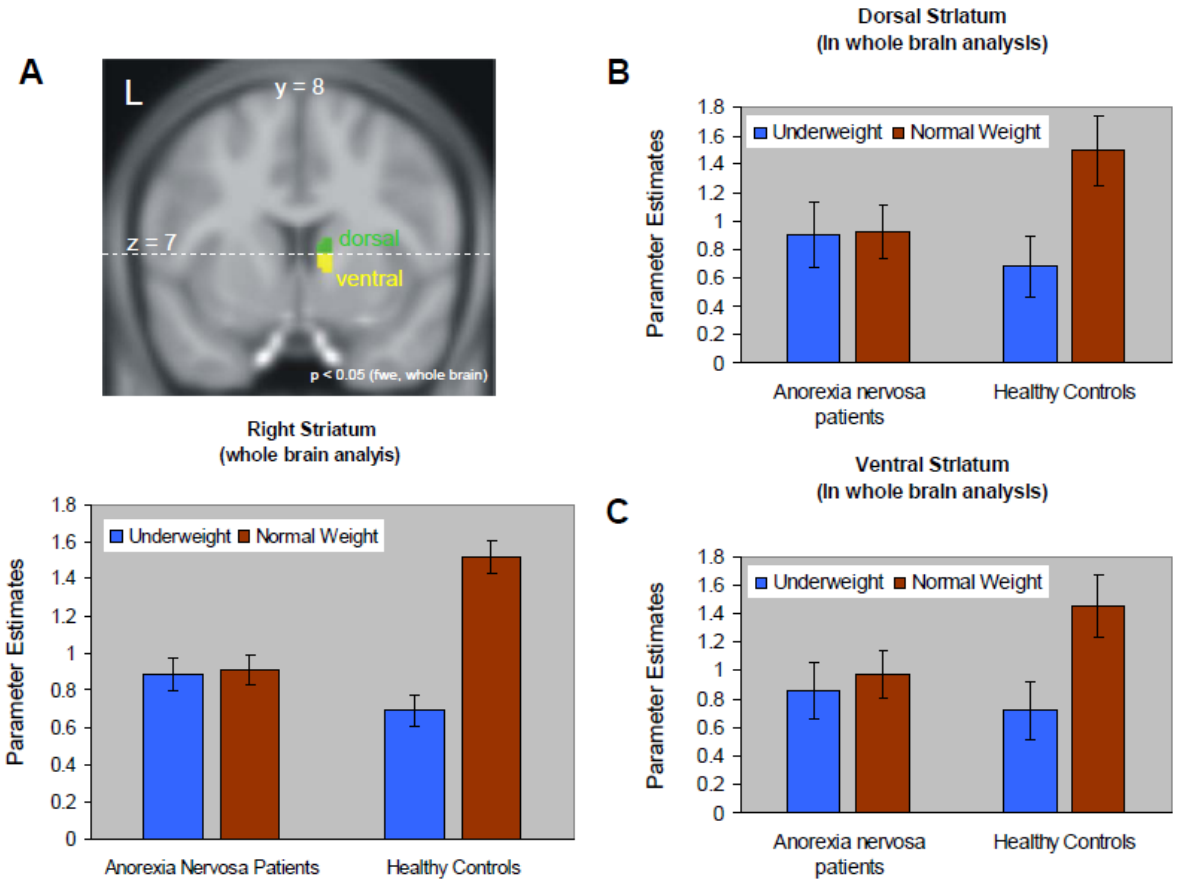
SF1. Mean effect sizes for group-by-stimulus interactions.

Results of the additional whole-brain analysis

A whole brain analysis with p-values adjusted for the entire brain as search volume ($p < 0.05$, FWE corrected) showed the right striatum significant for the relevant single-tailed group-by-stimulus interaction contrast (group differences contrasting neural activations upon underweight against normal weight stimuli obtained under the feel task instruction; Int 1). Peak voxel coordinates were: x = 10, y = 8, z = 8; z-score = 4.89, $p = 0.011$; cluster size 55 ($p = 0.001$; Figure SF2A).

The whole-brain analysis also showed that this interaction effect extended into the more dorsal parts of the striatum. Further analysis could show that 53 % (n = 29) of the significant voxels of the entire cluster were within the ventral striatum while 47 % (n = 26) of the significant voxels were located in the inferior parts of the dorsal striatum. The signal pattern in both parts of the striatum did not differ (see Figure SF2B and SF2C).

As for the ROI analysis in the main paper, post-hoc testing of between-group differences showed that controls' neural activity upon normal weight stimuli was significantly greater than that of patients ($p < 0.001$) while the numerically increased neural activity of the patient group upon underweight stimuli was not significantly different from controls ($p = 0.059$). Within-group post-hoc testing yielded significantly greater neural activity for normal weight compared to underweight stimuli in controls ($p < 0.001$) while neural activity for both weight categories was alike in anorexic patients ($p = 0.408$).

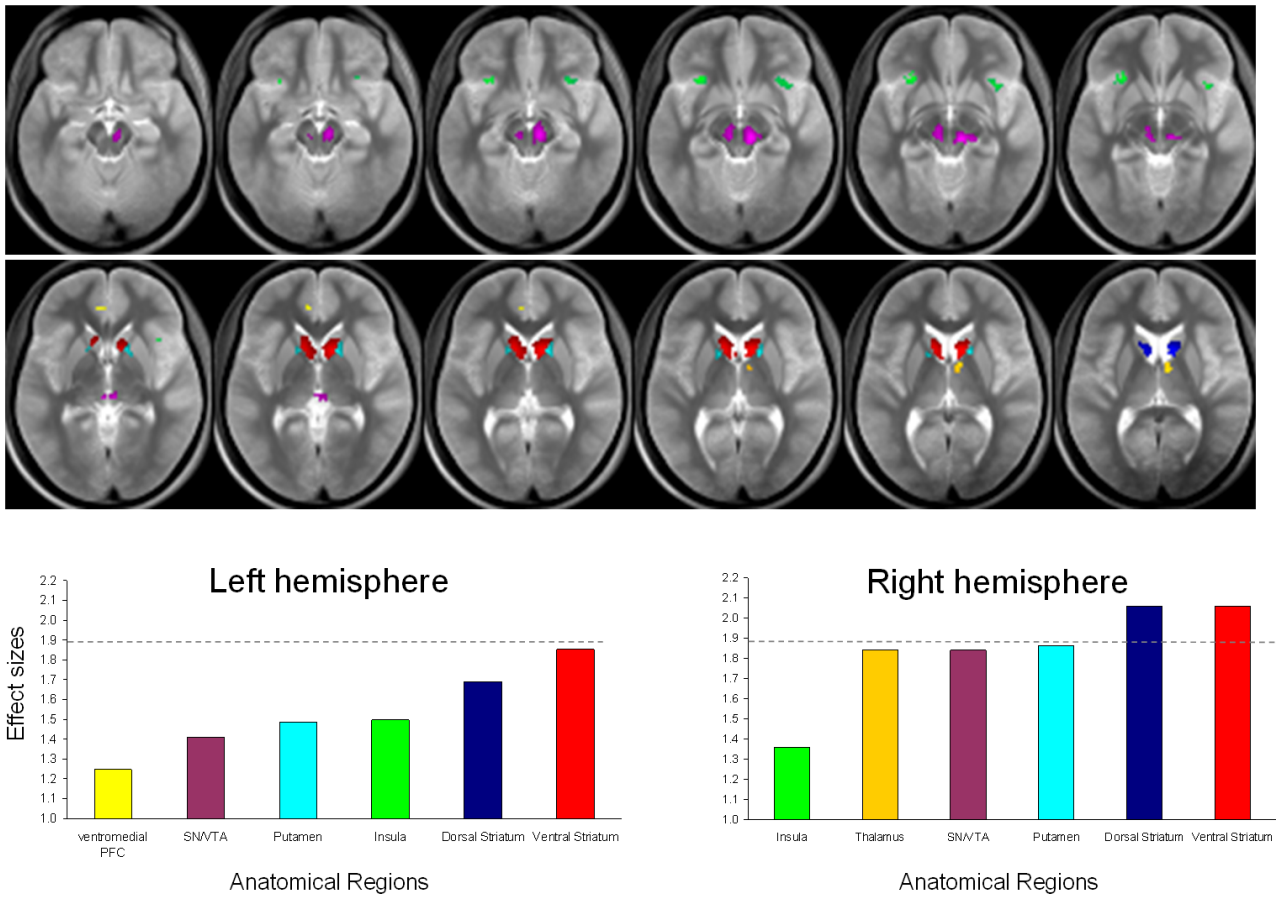


SF2. Bar plots of estimated neural activity upon underweight and normal weight stimuli averaged across significant voxels in A) the entire significant striatum and B) the dorsal and C) ventral areas of the striatum. (For the rationale of the ventral-dorsal border at z = 7 mm in the caudate see Supplemental Data accompanying Fladung AK et al. (2010) Am J Psychiat, 167:206-12; Postuma, RB & Dagher, A (2006). Cereb Cortex, 16: 1508-1521). Error is standard error of the mean.

Results of the additional extended ROI-based analysis

Since other brain regions are known to play a critical role in processing motivational salience or reward we additionally explored the relevant group-by-stimulus interaction contrast within a ROI-based approach at a more lenient statistical threshold than above. Based on an automated meta-analysis of 329 studies in the Neurosynth database (http://www.neurosynth.org/features/reward; see Yarkoni et al., 2011) that loaded highly on the feature "reward", brain regions were identified that were preferentially active for this specific feature (reverse inference map) and were consistently reported in the tables of those studies (forward inference maps). The corresponding brain maps were downloaded and a conjunction of both maps was used as an inclusive mask within which the effect of the group-by-stimulus interaction contrast was explored at a statistical threshold of $p < 0.005$,

uncorrected, in combination with a cluster extent of at least 10 contiguously significant voxels. To integrate the variance of the relevant interaction effect, corresponding effect sizes were calculated from the t-values of peak voxels (Rosenthal & Rosnow, 2008) of each anatomical region bearing a significant effect. Results are summarized in Figure SF3 and Table S1 below.



SF3. Color-coded brain regions bearing an exploratory significant effect of the relevant group-by-stimulus interaction at the significance level of $p < 0.005$, uncorrected, in combination with a cluster extent of at least 10 contiguously significant voxels. For better visibility of especially the subcortical regions, clusters were superimposed on an averaged MNI-normalized proton-density weighted MR image obtained from a different sample of 40 subjects. Bars represent the effect sizes calculated from the peak voxel's t-value of each cluster already taking into account the variance of the modeled interaction effects. The grey dashed line represents the critical effect size of $d = 1.898$ corresponding to a statistical threshold of $p < 0.05$, family-wise corrected for multiple comparisons. Estimated effect sizes of $d > 1.05$ represent significance at a level of $p < 0.005$ uncorrected. SN/VTA denotes the midbrain regions substantia nigra (SN) and ventral tegmental area (VTA). Insula denotes the anterior insula.

Table S1. MNI-coordinates (x,y,z) of peak voxels within each anatomical region-of-interest bearing a group-by-stimulus interaction effect at the level of significance of $p < 0.005$, uncorrected and a cluster size of at least 10 contiguously significant voxels.

Anatomical Region	Hemisphere	x	y	z	z-score	cluster size
ventromedial PFC	L	-6	40	-2	3.05	11
anterior Insula	L	-30	22	-10	3.63	48
	R	36	16	-6	3.31	53
Putamen	L	-14	8	2	3.61	19
	R	14	8	2	4.46	43
Thalamus	R	8	-8	12	4.42	39
Midbrain (SN/VTA)	L	-6	-26	-8	3.44	223
	R	8	-24	-10	4.41	
Dorsal Striatum	L	-10	8	8	4.07	35
	R	10	8	8	4.89	46
Ventral Striatum	L	-10	10	4	4.44	131
	R	10	8	6	4.89	134

L: left; R: right; PFC: prefrontal cortex; critical z-score to pass a significance threshold of $p < 0.05$, family-wise corrected for multiple comparisons: 4.54.

As can be seen from Figure S3 and Table S1 the critical threshold for the relevant group-by-stimulus interaction contrast was passed only in the right dorsal and ventral striatum as shown in the main paper. All other brain regions known to play a critical role in processing motivational salience or reward showed effects below this threshold. Besides the peak voxels in the right putamen and right thalamus also the peak voxel within the right midbrain area comprising the SN/VTA complex fell short below the critical effect size corresponding to a threshold of $p < 0.05$, FWE-corrected.

References:

Yarkoni T, Poldrack RA, Nichols TE, Van Essen DC, Wager TD. Large-scale automated synthesis of human functional neuroimaging data. *Nat Methods 2011;* **8:** 665-70.

Rosenthal R and Rosnow RL. *Essentials of Behavioral Research: Methods and Data Analysis, 3rd Edition*. McGraw-Hill: New York, USA, 2008.