Appendix 1 to Ehrlich S, Geisler D, Ritschel F, et al. Elevated cognitive control over reward processing in recovered female patients with anorexia nervosa.

J Psychiatry Neurosci 2015.

DOI: 10.1503/jpn. 140249

Supplementary methods

Participants

Recovered participants were recruited from the specialized eating disorder programs of a university child and adolescent psychiatry and psychosomatic medicine department and diagnosed using the expert version of a semi-structured research interview, the Structured Interview for Anorexia and Bulimia Nervosa for DSM-IV (SIAB-EX, see below). Within the recovered group 23 (77%) of the patients were of the restrictive and 7 (23%) of the binge/purging subtype. To be considered restrictive, recovered participants were required to have never met criteria for the binge/purging subtype. None of the recovered participants were receiving psychiatric or psychotherapeutic care at the time of study. During the acute stage of their illness all participants had been treated as inpatients; most had also received outpatient care before and/or after hospitalization.

Healthy controls were recruited through advertisement among middle school, high school and university students.

Inclusion criteria (e.g. the absence of significant restrictive eating patterns or binge–purge behavior), exclusion criteria (e.g. the use of psychotropic medications) and other possibly confounding variables were obtained using the SIAB-EX and our own semistructured interview. "Regular" binge eating was defined as having 1 objective binge eating episode at least once weekly for 3 or more consecutive months.

At the time of our study none of the participants had an active psychiatric condition ascertained using a semistructured in-house research interview and the expert version of the SIAB-EX. All interviews were carried out by trained graduate students (psychology or medicine). If there were any indications of persisting or new psychiatric symptoms each case was discussed with a fully board-certified expert clinician, and assessments were extended if necessary. Comorbid diagnoses at the time of treatment (i.e., in the past) were taken according to standard practice from medical records and confirmed by an expert clinician with more than 10 years' experience after careful chart review (including consideration of medical and psychiatric history, physical examination, routine blood tests, urine analysis and a range of psychiatric screening instruments (e.g., SIAB-EX, EDI-2, BDI-II; SCL-90-R). In the recovered group 7 participants had associated psychiatric comorbidity at the time of treatment (6 depressive disorders and 1 obsessive compulsive disorder).

Control participants were excluded if they had any history of psychiatric illness, a lifetime body mass index (BMI) below the tenth age percentile (if < 18 yr)/BMI below 18.5kg/m^2 (if > 18 yr), or were currently obese (BMI not over 97th age percentile if < 18 yr; BMI not over 30kg/m^2 if > 18 yr). Participants of all study groups were excluded if they had a lifetime history of any of the following clinical diagnoses: organic brain syndrome, schizophrenia, substance dependence, psychosis not otherwise specified, bipolar disorder, bulimia nervosa or binge-eating disorder (or "regular" binge eating, defined as bingeing at least once weekly for 3 or more consecutive months). Further exclusion criteria for all participants were IQ lower than 85; psychotropic medication within 6 weeks prior to the study; current substance abuse; current inflammatory, neurologic or metabolic illness; chronic medical or neurological illness that could affect appetite, eating behaviour, or body weight (e.g., diabetes); clinically relevant anemia; pregnancy; and breastfeeding.

Study data were collected and managed using the secure, web-based electronic data capture tool REDCap (Research Electronic Data Capture[1]).

Clinical measures

For all participants current and/or past diagnoses of eating disorders were evaluated using the expert form of the SIAB (SIAB-EX[2]), a well-validated 87-item semistandardized interview that assesses the prevalence and severity of specific eating-related psychopathology over the past 3 months. The interview provides diagnoses according to the ICD-10 and DSM-IV and is suitable for adolescents as well as adults. Interviews were conducted by clinically experienced and trained graduate students under the supervision of the attending child and adolescent psychiatrist.

Appendix 1 to Ehrlich S, Geisler D, Ritschel F, et al. Elevated cognitive control over reward processing in recovered female patients with anorexia nervosa.

J Psychiatry Neurosci 2015.

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IQ was assessed with a short version of the German adaption of the Wechsler Adult Intelligence Scale[3] for participants aged 16 years and older or a short version of the German adaption of the Wechsler Intelligence Scale for Children[4] for participants aged 15 years or younger.

Socioeconomic status (SES) was estimated according to standard practice on the basis of parental education level.

Instrumental motivation task

This task variant also provides behavioural assessment of motivation operationalized as instrumental responding to maximize reward.[5,6] Instrumental responding is measured via the number of button presses and reaction times (RT) in the motor (or instrumental) response phase of the task. RT was defined as the time elapsing between the beginning of the appearance of the visual stimulus (exclamation mark) and the beginning of a participant's reaction to it (first button press) in milliseconds.

Before the scanning session, participants completed a practice version of the task (12 trials) to learn how to perform it.

Structural and functional image acquisition

Structural and functional MRI data were acquired with a 3 T scanner (Magnetom Trio, Siemens).

The T_1-weighted structural brain scans were acquired with rapid acquisition gradient echo (MP-RAGE) sequence with the following parameters: number of slices = 176; repetition time (TR) 1900 ms; echo time (TE) 2.26 ms; flip angle 9°; slice thickness 1 mm; voxel size $1 \times 1 \times 1$ mm³; field of view (FOV) 256×224 mm²; bandwidth 200 Hz/pixel.

The functional images were acquired using gradient-echo T_2*-weighted echo planar imaging (EPI) with the following parameters: tilted 17° from anterior–posterior commissure line toward coronal (to reduce signal dropout in orbitofrontal regions); number of volumes = 396; number of slices = 42; TR 2410 ms; TE 25 ms; flip angle 80°; 3 mm in-plane resolution; slice thickness 2 mm (1 mm gap resulting in a voxel size of $3 \times 3 \times 2$ mm³); FOV 192×192 mm²; bandwidth 2112 Hz/pixel.

Functional image data processing and analysis

The slice time corrected functional EPI data were realigned and registered to their mean. The 6 realignment parameters, characterizing the rigid-body movement (*x,y,z*, pitch, roll, yaw), were saved and later used as nuisance covariates to account for the variance due to motion. Subsequently these images were coregistered to the participant's structural brain image. A DARTEL template was created using structural images from all participants.[7] The EPI volumes were then normalized to Montreal Neurological Institute space using the DARTEL template and corresponding flow field. The resulting data were smoothed with an isotropic 8 mm full-width at half-maximum Gaussian kernel. During the image data processing at the single participant-level using a general linear model (GLM), all regressors were convolved with a synthetic hemodynamic response function as implemented in SPM8.

We evaluated the quality of the fMRI data by manual inspection and using artifact detection tools (ART).[8] Volumes that exceeded an intensity threshold of 3 standard deviations (SD) or a threshold of 2 mm normalized movement in any direction were classified as outliers and discarded in the statistical analysis using additional regressors in the GLM (motion outlier: 1.14 ± 2.73 in recovered patients and 1.48 ± 4.12 in controls; intensity outlier: 5.48 ± 2.74 in recovered patients and 4.90 ± 3.07 in controls); the 2 groups did not differ regarding numbers of motion and intensity outliers (motion outlier: $t_{58} = 0.33$; $p > 0.1$; intensity-outlier: $t_{68} = 0.69$; $p > 0.1$).

To extract data from single participant-level contrast maps we used a priori regions of interest (ROI). The mask of the ventral striatum was specified by binarizing a probabilistic map[9] with a threshold value of 0.4. The mOFC mask was created by merging the left and right frontal medial orbital cortex label from the Automated Anatomical Labelling (AAL) atlas provided in the Wake Forest University (WFU) PickAtlas for SPM.[10,11] For the left and right DLPFC masks we merged the regions of superior and middle frontal gyrus in the WFU PickAtlas for the left and the right hemisphere, respectively, but excluded posterior parts with $y < 24$ in MNI space (as in our previous work[12,13]).

Appendix 1 to Ehrlich S, Geisler D, Ritschel F, et al. Elevated cognitive control over reward processing in recovered female patients with anorexia nervosa.

J Psychiatry Neurosci 2015.

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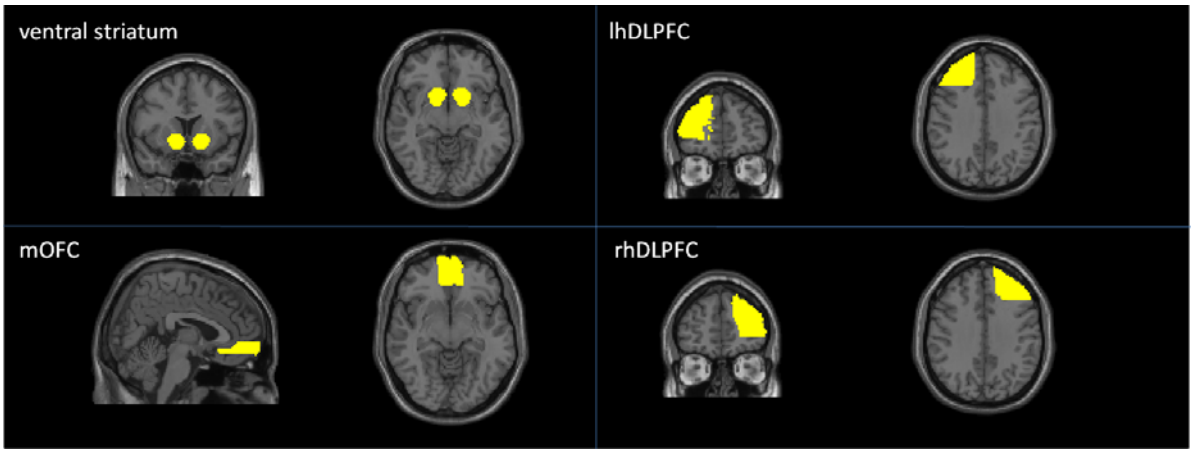

Fig. S1: A priori regions of interest.

Analogue to the analysis strategy applied to the behavioural instrumental response data, we analyzed the extracted indices of neural responses using linear mixed models in SPSS version 21.0. We assumed a compound symmetry covariance structure for the reward level–dependent change of the hemodynamic response (0, 1, 10, 100 — all centred, see Methods) and included a main effect of group (recovered and control as a factor with control as a reference) as well as an interaction effect (slope) between group and reward level. Extracted data from the left and right DLPFC were modelled together using "hemisphere" as an additional within-subjects factor.

Since the phase of menstrual cycle was reported to modulate reward processing,[14] we ran additional mixed models using the self-reported phase of menstrual cycle as another fixed effect. The variable used for menstrual cycle had 2 levels according to the presumed hormonal situation: follicular phase (high estradiol) or luteal phase (high estradiol and progesterone).[15]

In addition, exploratory whole brain group-level analyses were performed in SPM8. In order to report main effects of task across all participants, we used a family-wise error (FWE)–corrected threshold of $p < 0.05$ based on random field theory and a minimum cluster size of ≥ 10 voxels.[16] For the between-group contrast maps, voxels surviving a combined threshold of $p < 0.005$ and cluster size (in voxels) of ≥ 33 for the ventral striatum, ≥ 39 for the mOFC, ≥ 135 for the left DLPFC and ≥ 141 for the right DLPFC, which corresponds to a corrected FWE threshold of $p < 0.05$ (based on results of Monte Carlo simulations using the AFNI program 3dClustSim; http://afni.nimh.nih.gov/pub/dist/doc/program_help/3dClustSim.html), were considered to show statistically significant group differences. The same contrast maps were also explored at a whole-brain level; here we limited detailed data reporting only to voxels surviving a combined threshold of $p < 0.005$ and cluster size $\geq$ 783 voxels, which corresponds to a corrected FWE threshold of $p < 0.05$. Brain regions were labelled according to the AAL atlas.[17]

Additional statistical analyses

Demographic and symptom variables were compared using Student *t* tests. Correlational analyses were performed using Pearson coefficients. In all statistical analyses we used age-adjusted BMI SD scores (BMI-SDS; calculated using

Appendix 1 to Ehrlich S, Geisler D, Ritschel F, et al. Elevated cognitive control over reward processing in recovered female patients with anorexia nervosa.

J Psychiatry Neurosci 2015.

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the least squared means method from Cole (1990) and German population reference data from Kromeyer-Hauschild et al., 2001 [for participants ≤ 18 yr old] and Hemmelmann et al., 2010 [for participants ≥ 19 yr old]).[18-20]

If not indicated otherwise, all values are presented as means ± SD.

Supplementary results

Table S1: β estimates and test statistics for the mixed models using left and right DLPFC respose as the dependent variable

Dependent variable	Parameter	β estimate	SE	Statistic	*p* value
Anticipation-related left and right DLPFC response	Reward level	0.43	0.09	$t_{420} = 4.71$	< 0.001
	Hemisphere	0.23	0.15	$t_{420} = 1.55$	0.12
	Diagnostic group (recovered)	1.42	0.67	$t_{60} = 2.14$	0.036
	Diagnostic group (recovered) × reward level	0.15	0.13	$t_{420} = 1.19$	0.24
Feedback-related left and right DLPFC response	Reward level	–0.56	0.09	$t_{420} = –5.94$	< 0.001
	Hemisphere	–0.15	0.15	$t_{420} = –0.99$	0.32
	Diagnostic group (recovered)	0.39	0.34	$t_{60} = 1.16$	0.25
	Diagnostic group (recovered) × reward level	0.44	0.13	$t_{420} = 3.25$	0.001

DLPFC = dorsolateral prefrontal cortex; SE = standard error.

Table S2: Anticipatory brain activity at the average reward level (typical response) of all participants*

		MNI space; local maximum, mm			
Brain region†	Cluster size	*x*	*y*	*z*	Peak T_{max}
R inferior occipital gyrus	432	46	–62	–12	15.36
R fusiform gyrus	—	28	–68	–8	15.18
R hemispheric lobule VIIB	230	34	–72	–50	8.27
L middle temporal gyrus	121	–60	–2	–12	5.96
L middle temporal gyrus	—	–58	4	–18	5.87
L cerebellum hemispheric lobule IX	44	–12	–48	–48	5.84
L medial superior frontal gyrus	73	–4	64	26	5.72
L medial superior frontal gyrus	—	–10	60	36	5.05
Temporal pole, L middle temporal gyrus	90	–52	12	–28	5.59
Temporal pole, L middle temporal gyrus	—	–34	14	–36	5.38
L inferior temporal gyrus	—	–44	8	–34	5.34
R paracentral lobule	29	–12	–22	68	5.57
R medial superior frontal gyrus	166	2	36	54	5.33
L medial superior frontal gyrus	—	0	44	48	5.27
R medial superior frontal gyrus	—	10	50	42	5.11
L orbital inferior frontal gyrus	15	–46	42	–18	5.32
R orbital middle frontal gyrus	18	48	52	–8	5.28
L anterior cingulate and paragingulate gyri	10	–4	6	28	5.24

AAL = automated anatomical labeling; FWE = family-wise error; L = left; MNI = Montreal Neurological Institute; R = right.
*Local maxima of suprathreshold activation clusters and corresponding *t* values FWE-corrected at $p < 0.05$ (corrected for the entire brain volume) and $k \geq 10$. All local maxima within significant clusters are reported.
†Labelled according to the AAL atlas.

Appendix 1 to Ehrlich S, Geisler D, Ritschel F, et al. Elevated cognitive control over reward processing in recovered female patients with anorexia nervosa.

J Psychiatry Neurosci 2015.

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Table S3: Increased anticipatory neural response at the average reward level (typical response) in recovered patients compared with controls in a whole-brain analysis*

		MNI space; local maximum, mm			
Brain region†	Cluster size	*x*	*y*	*z*	Peak T_{max}
R supplementary motor area	9415	14	–20	50	4.26
R precentral gyrus	—	36	–16	44	3.83
L supplementary motor area	—	–12	14	58	3.83
L rolandic operculum	1136	–58	–2	12	4.14
L triangular inferior frontal gyrus	—	–42	20	10	4.1

AAL = automated anatomical labeling; L = left; MNI = Montreal Neurological Institute; R = right.
*Local maxima of suprathreshold (at $p < 0.005$ and $k \geq 738$, which corresponds to a corrected threshold of $p < 0.05$) activation clusters and corresponding *t* values. All local maxima within significant clusters are reported.
†Labelled according to the AAL atlas.

Table S4: Feedback-related reward-level-dependent neural response (slope) across all participants*

		MNI space; local maximum, mm				
Brain region†	Cluster size	*x*	*y*	*z*	Cluster p_{FWE}	Peak T_{max}
Right inferior parietal lobule (excluding supramarginal and angular gyri)	14	56	–34	56	0.011	6.03
Vermic lobule VI	10	0	–54	–22	0.015	5.21

AAL = automated anatomical labeling; FWE = family-wise error; L = left; MNI = Montreal Neurological Institute; R = right.
*Local maxima of suprathreshold ($p_{FWE} < 0.05$ [corrected for the entire brain volume] and $k \geq 10$) activation clusters and corresponding *t* values.
†Labelled according to the AAL atlas.

Table S5: Functional connectivity analysis — bivariate correlations between the timecourses between selected regions of interest*

	MNI coordinates			Group; mean *r* ± SEM			
Region of interest	*x*	*y*	*z*	Recovered patients	Control	Statistic	*p* value
L DLPFC, L ventral striatum	–35 20	40 12	38 0	0.33 ± 0.03	0.31 ± 0.03	$t_{58} = 0.417$	0.68
L DLPFC, R ventral striatum	–36 24	40 14	38 –8	0.24 ± 0.03	0.23 ± 0.03	$t_{58} = 0.255$	0.80
L DLPFC, mOFC	–36 10	40 52	38 –10	0.26 ± 0.03	0.10 ± 0.03	$t_{58} = 3.530$	0.001

DLPFC = dorsolateral prefrontal cortex; L = left; MNI = Montreal Neurological Institute; mOFC = medial orbitofrontal cortex; R = right; SEM = standard error of the mean.
*Timecourses (first eigenvariate) were adjusted for effects of interest (i.e. task and motion parameters). Correlations were standardized using Fisher *r–z* transformation and compared between groups using Student *t* tests.

Appendix 1 to Ehrlich S, Geisler D, Ritschel F, et al. Elevated cognitive control over reward processing in recovered female patients with anorexia nervosa.

J Psychiatry Neurosci 2015.

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Table S6: Correlations between behavioral measures (no. of button presses, reaction time) and reward anticipation–related left and right DLPFC activity at each reward level in recovered patients and healthy controls*

	No. Of button presses; *r* (*p* value)				Reaction time; *r* (*p* value)			
Group, reward level	Cue 0	Cue 1	Cue 10	Cue 100	Cue 0	Cue 1	Cue 10	Cue 100
Recovered L DLFPC	0.43 (0.017)	0.42 (0.019)	0.39 (0.034)	0.54 (0.002)	–0.49 (0.006)	–0.30 (0.10)	–0.26 (0.17)	–0.23 (0.22)
Recovered R DLFPC	0.44 (0.015)	0.42 (0.020)	0.42 (0.021)	0.59 (0.001)	–0.47 (0.009)	–0.31 (0.09)	–0.24 (0.19)	–0.22 (0.25)
Control L DLFPC	0.38 (0.034)	0.08 (0.69)	0.17 (0.36)	0.23 (0.21)	–0.29 (0.11)	–0.21 (0.26)	–0.05 (0.81)	–0.14 (0.45)
Control R DLFPC	0.47 (0.008)	0.18 (0.34)	0.11 (0.56)	0.35 (0.06)	–0.31 (0.10)	–0.34 (0.07)	–0.19 (0.32)	–0.29 (0.11)

DLPFC = dorsolateral prefrontal cortex; L = left; R = right.
*In the recovered group the no. of button presses at each reward level correlated positively with L and R DLPFC activity during the anticipation phase at the corresponding reward levels. In contrast, this relationship was significant only at reward level 0 in controls. For reaction time, the correlations were negative with a similar pattern although somewhat less pronounced.

Table S7: Correlations between additional clinical variables and behavioural responses, neural responses at the average reward level ("typical response") during reward anticipation in any of the ROIs, change of neural responses across reward levels during feedback in any of the ROIs and to node-node connectivity during the anticipation and feedback phase of the motivational task

	Clinical variable; *r* (*p* value)			
Behavioural response	Drive for thinness	Depressive symptoms	Anxiety symptoms	Length of recovery
Typical no. of button presses	0.04 (0.85)	0.27 (0.16)	0.25 (0.20)	0.06 (0.80)
Typical RT	–0.36 (0.07)	–0.31 (0.10)	–0.20 (0.31)	0.19 (0.38)
Change in no. of button presses	–0.06 (0.77)	0.04 (0.83)	–0.24 (0.21)	–0.03 (0.91)
Change in RT	0.27 (0.18)	0.11 (0.56)	0.17 (0.38)	0.02 (0.94)
Typical L DLPFC response (anticipation)	–0.04 (0.83)	0.02 (0.93)	–0.14 (0.47)	–0.14 (0.51)
Typical R DLPFC response (anticipation)	–0.02 (0.91)	0.00 (0.99)	–0.17 (0.39)	–0.12 (0.59)
Typical ventral striatal response (anticipation)	–0.12 (0.58)	–0.04 (0.86)	–0.24 (0.21)	–0.10 (0.65)
Typical VMPFC response (anticipation)	–0.07 (0.74)	–0.02 (0.92)	–0.22 (0.25)	–0.21 (0.35)
Change in lhDLPFC response (feedback)	–0.14 (0.49)	–0.27 (0.16)	–0.14 (0.46)	–0.14 (0.52)
Change in rhDLPFC response (feedback)	–0.26 (0.19)	–0.33 (0.08)	–0.17 (0.37)	–0.22 (0.32)
Change in ventral striatal response (feedback)	–0.03 (0.88)	0.07 (0.72)	–0.15 (0.44)	–0.18 (0.42)
Change in VMPFC response (feedback)	0.09 (0.65)	–0.04 (0.85)	–0.30 (0.11)	–0.25 (0.25)
L DLPFC–R ventral striatum connectivity	–0.16 (0.44)	–0.07 (0.71)	–0.20 (0.30)	0.24 (0.26)
L DLPFC–L ventral striatum connectivity	–0.16 (0.43)	–0.05 (0.80)	–0.19 (0.33)	0.25 (0.26)
L DLPFC–L VMPFC connectivity	–0.06 (0.76)	–0.04 (0.85)	–0.05 (0.80)	0.14 (0.53)

BDI = Beck Depression Inventory; DLPFC = dorsolateral prefrontal cortex; EDI = Eating Disorders Inventory; L = left; R = right; ROI = region of interest; RT = reaction time; SCL = Symptom Checklist Revised; VMPFC = ventromedial prefrontal cortex.
*The following clinical measures were used: EDI-2: drive for thinness; BDI-II: depressive symptoms; SCL-90-R: anxiety symptoms; length of recovery (in months).

Appendix 1 to Ehrlich S, Geisler D, Ritschel F, et al. Elevated cognitive control over reward processing in recovered female patients with anorexia nervosa.

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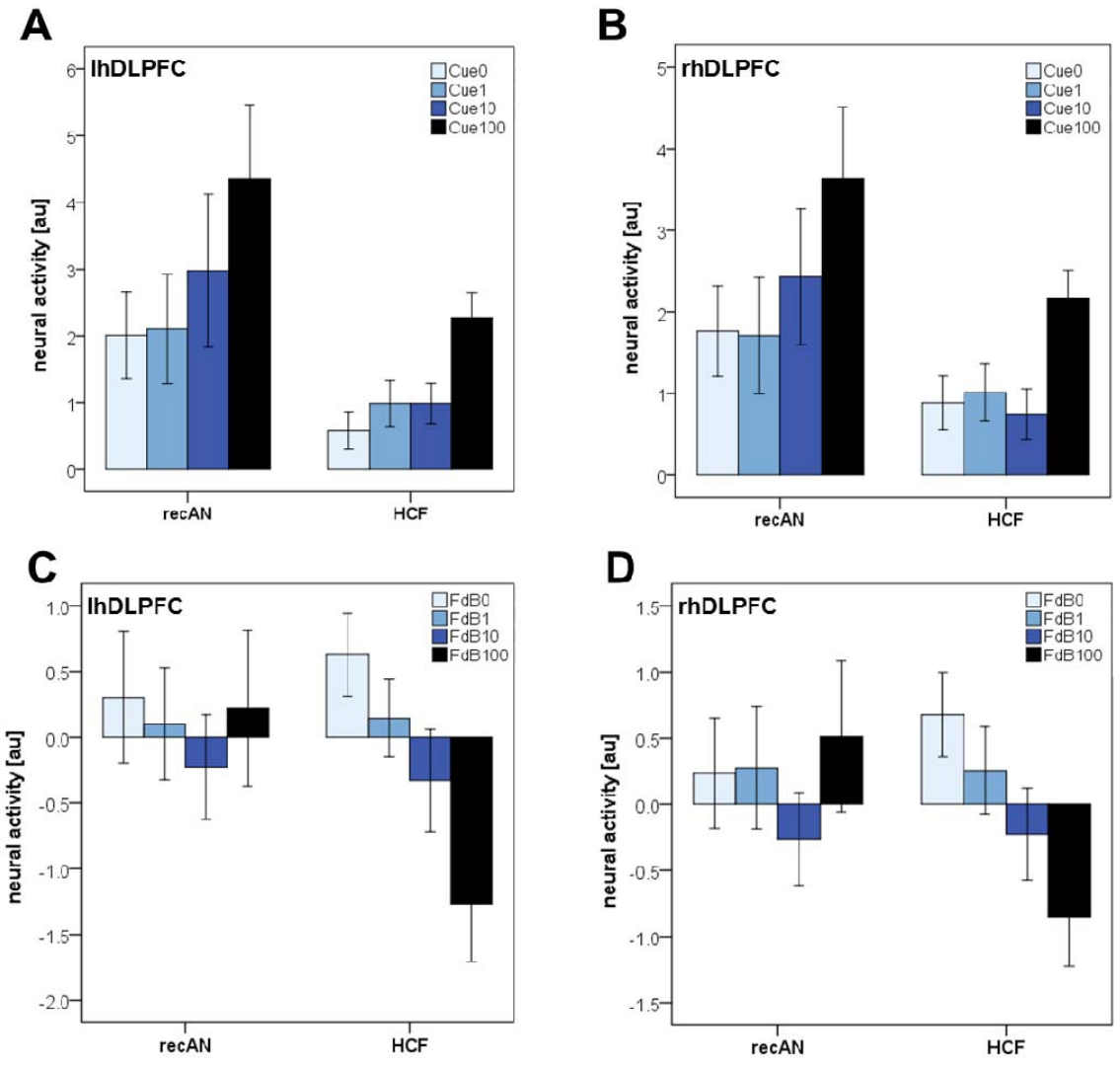

Fig. S2: Cue-related (i.e. reward anticipation, "Cue", A,B) and feedback-related (i.e. reward reception, "FdB", C,D) brain activity in response to varying monetary stimuli in the dorsolateral prefrontal cortex (DLPFC) in recovered patients with restrictive anorexia nervosa (recAN; *n* = 23) and healthy controls (HCF). Blood oxygen level-dependent response data of the left (lh)DLPFC (A,C) and right (rh)DLPFC (B,D) are depicted across the different reward levels (mean β ± standard error of the mean).

Appendix 1 to Ehrlich S, Geisler D, Ritschel F, et al. Elevated cognitive control over reward processing in recovered female patients with anorexia nervosa.

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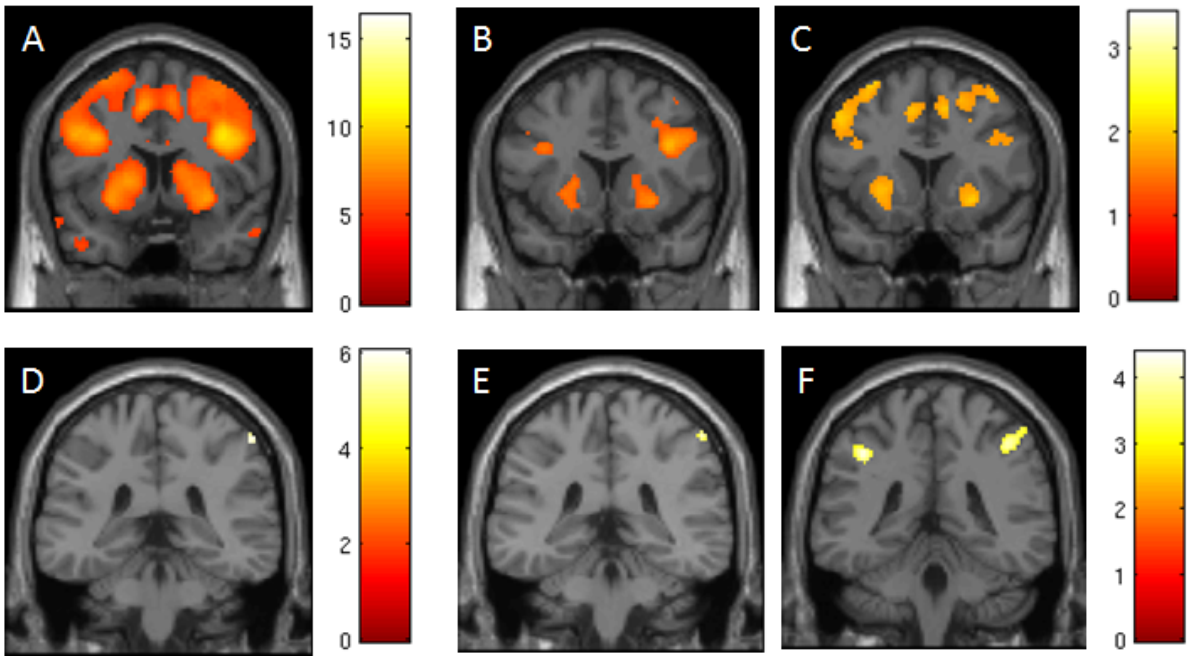

Fig. S3: Main effects in the instrumental motivation task. Cue-related (i.e. reward anticipation) brain activity at the average reward level (typical response) is depicted in the panels A (all participants), B (controls) and C (recovered patients). Feedback-related (i.e. reward receipt) brain activity (slope, i.e. reward-level dependent) is depicted in the panels D (all participants), E (controls) and F (recovered patients). Statistical parametric maps (presented in neurological convention) were overlaid on a template T_1-weighted MRI scan at $p < 0.05$ (family-wise error–corrected for the entire brain volume) and $k \geq 10$ for A and D (all participants) and at $p < 0.001$ (uncorrected) and $k \geq 25$ for all other panels.

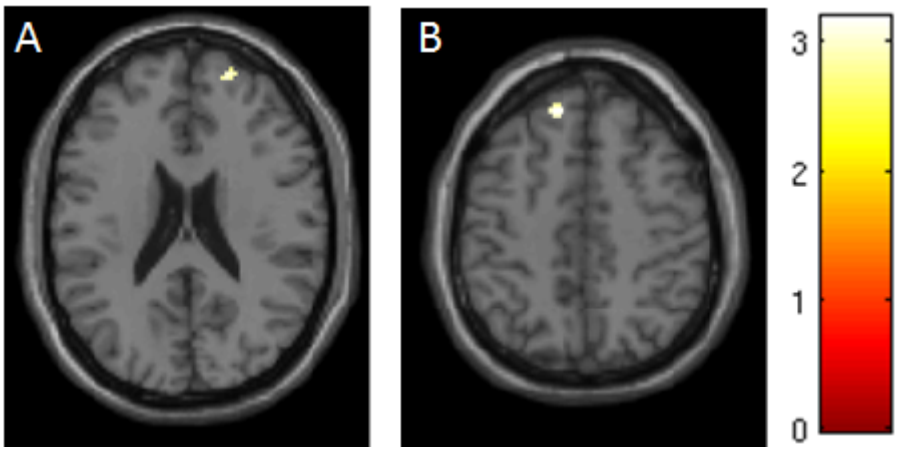

Fig. S4: Group differences (recovered patients > control) not surviving the conservative threshold used in our main analysis. (A) Increased cue-related (i.e. reward anticipation) brain activity at the average reward level (typical response) in recovered patients compared with controls in the right dorsolateral prefrontal cortex (DLPFC) and (B) increased feedback-related (i.e. reward receipt) brain activity (slope, i.e. reward-level dependent) in recovered patients compared with controls in the left DLPFC. Statistical parametric maps (presented in neurological convention) were overlaid on a template T_1-weighted MRI scan at $p < 0.005$ (uncorrected) and $k > 0$.

Appendix 1 to Ehrlich S, Geisler D, Ritschel F, et al. Elevated cognitive control over reward processing in recovered female patients with anorexia nervosa.

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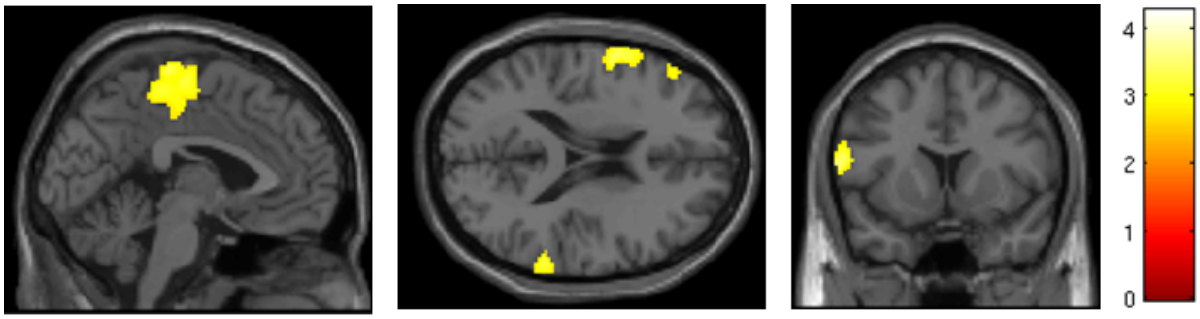

Fig. S5: Increased cue-related (i.e. reward anticipation) brain activity at the average reward level (typical response) in recovered patients compared with controls in areas other than the dorsolateral prefrontal cortex. Statistical parametric maps (presented in neurological convention) were overlaid on a template T_1-weighted MRI scan at $p < 0.005$ and $k \geq 738$, which corresponds to a corrected threshold of $p < 0.05$ (corrected for the entire brain volume).

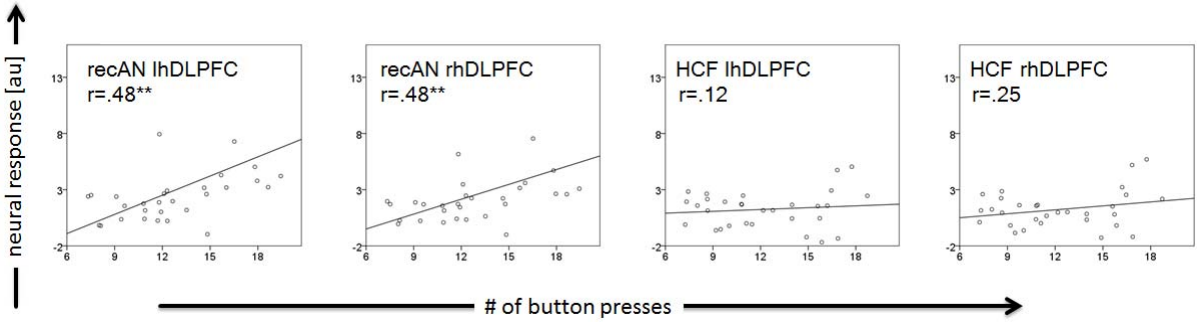

Fig. S6: Coupling between behavioural responses and left (lh) and right (rh) dorsolateral prefrontal cortex (DLPFC) activity in the two groups. Correlations (**$p < 0.01$) between the typical number of button presses during the anticipation of monetary reward and the typical anticipatory left and right DLPFC activity at the average reward level (typical response).

Supplementary discussion

Additional statistical analyses

Feedback about monetary reward could also be expected to elicit increased neural responses. However, within the framework of this task it has been shown previously that the feedback phase is associated with reward-level dependent decreases in neural responses (see also Fig. 6 in Kroemer et al., 2014[6]). This is due to the highly deterministic nature of this task. Although participants win more money if they press the button more often, the trial-by-trial fluctuations in instrumental responses are much lower than the 10-fold differences between the reward levels. Hence, the expected monetary reward can be predicted based on the information on the reward level at the cue onset of each trial. Critically, the initial training, which takes place before the main experiment starts, is sufficient in providing a good estimate for expected reward, which reduces reinforcement learning throughout the task. Reward-level dependent deactivations during the feedback phase occur because deactivations are stronger if anticipatory brain responses are stronger.[6] Notably, in the "classic" variant of the monetary incentive delay task, nonreward trials were characterized by higher feedback responses compared to all reward trials in the putamen and orbitofrontal cortex[21] as well, highlighting that this effect is not specific to our paradigm.

Appendix 1 to Ehrlich S, Geisler D, Ritschel F, et al. Elevated cognitive control over reward processing in recovered female patients with anorexia nervosa.

J Psychiatry Neurosci 2015.

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Appendix 1 to Ehrlich S, Geisler D, Ritschel F, et al. Elevated cognitive control over reward processing in recovered female patients with anorexia nervosa.

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