Research paper

Elevated cognitive control over reward processing in recovered female patients with anorexia nervosa

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Background: Individuals with anorexia nervosa are thought to exert excessive self-control to inhibit primary drives. **Methods:** This study used functional MRI (fMRI) to interrogate interactions between the neural correlates of cognitive control and motivational processes in the brain reward system during the anticipation of monetary reward and reward-related feedback. In order to avoid confounding effects of undernutrition, we studied female participants recovered from anorexia nervosa and closely matched healthy female controls. The fMRI analysis (including node-to-node functional connectivity) followed a region of interest approach based on models of the brain reward system and cognitive control regions implicated in anorexia nervosa: the ventral striatum, medial orbitofrontal cortex (mOFC) and dorsolateral prefrontal cortex (DLPFC). **Results:** We included 30 recovered patients and 30 controls in our study. There were no behavioural differences and no differences in hemodynamic responses of the ventral striatum and the mOFC in the 2 phases of the task. However, relative to controls, recovered patients showed elevated DLPFC activity during the anticipation phase, failed to deactivate this region during the feedback phase and displayed greater functional coupling between the DLPFC and mOFC. Recovered patients also had stronger associations than controls between anticipation-related DLPFC responses and instrumental responding. **Limitations:** The results we obtained using monetary stimuli might not generalize to other forms of reward. **Conclusion:** Unaltered neural responses in ventral limbic reward networks but increased recruitment of and connectivity with lateral–frontal brain circuitry in recovered patients suggests an elevated degree of self-regulatory processes in response to rewarding stimuli. An imbalance between brain systems subserving bottom–up and top–down processes may be a trait marker of the disorder.

Introduction

Anorexia nervosa is an eating disorder that commonly begins during early adolescence in girls and is characterized by relentless pursuit to lose weight, mostly by self-starvation. Mortality associated with anorexia nervosa is among the highest in psychiatry.[1] Genetic heritability is estimated to account for about 50%–80% of the risk for anorexia nervosa,[2] but the limited understanding of the underlying pathophysiology of this devastating illness has hindered the development of effective treatments.[3]

Primary rewards (food, sex, pleasant touch) are often described as unpleasant and avoided by patients with anorexia nervosa.[4–9] Therefore, recent research has focused on the dopaminergic reward system, which includes mesocorticolimbic regions, such as the ventral striatum and orbitofrontal cortex (OFC). While early functional MRI (fMRI) studies found undifferentiated neural responses to monetary loss and reward in the ventral striatum[10] and reduced responses to sweet taste[11] in patients recovered from anorexia nervosa compared with healthy controls, later studies reported increased responses in reward-related brain regions in response to food- and disease-associated body stimuli.[12,13] These heterogeneous results might be due to differences in study design or small sample sizes ($n < 20$ per group). Furthermore, it is critical to differentiate between anticipation and receipt of reward (consummatory phase), since animal studies have shown that following stimulus conditioning, dopaminergic neurons shift firing from the receipt to the anticipation of reward or to cues predicting reward.[14] Reward tasks, such as the monetary incentive delay task using response speed[15] and the instrumental motivation task using

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response vigor,[16] as measures of motivation allow for separation of these components.

One of the most puzzling questions regarding anorexia nervosa is how patients are able to withstand the drive to eat despite an extremely low body mass index (BMI), while others struggle to maintain their weight or lose weight.[17] Studies in healthy controls have emphasized the association between cognitive control, eating and weight. For example, the ability to inhibit responses as measured by a stop-signal task and preference for snack foods interacted with their effect on weight change during a 1-year follow-up period — that is, participants with less effective response inhibition gained more weight.[18] Another study[19] suggested that OFC integrates competing goal values when choosing between healthy and tasty food and that this process is modulated by the dorsolateral prefrontal cortex (DLPFC) — one of the core areas of the cognitive control system.[20,21] The role of the DLPFC as a key regulator in cognitive control of food choice is also underlined by results of a recent repetitive transcranial magnetic stimulation (TMS) study that demonstrated changed preference ratings for high-caloric food items after inhibitory TMS of the DLPFC.[22]

Patients with anorexia nervosa tend to be over-controlled and show perseverative, obsessive and rigid thinking styles as well as personality characteristics such as low impulsivity and high harm avoidance.[23] Neuropsychological data[24] provide additional evidence of reduced cognitive flexibility and weak central coherence (i.e., an excessively detailed information-processing style). Studies have suggested that at least some of these characteristics are premorbid childhood traits and persist after recovery.[23,25] Such findings are consistent with the view of anorexia nervosa as a neurobiologically based disorder with abnormal higher-order cognitive control functions.

Some fMRI studies of patients with anorexia nervosa indicate alterations in frontoparietal networks involved in cognitive control and executive functions[26,27] as well as the engagement of these networks during incentive processing and motivation-related tasks that predominantly recruit limbic structures when performed by healthy individuals.[10,28–30] Taken together, these studies suggest that anorexia nervosa may be characterized by a dominance of executive brain circuits, perhaps as a mechanism to predict and control anxiety produced by certain stimuli or by the possibility of failure.[31]

The aims of the present study were two-fold: Given the sparse and contradictory literature on reward processing in patients with anorexia nervosa, we first wanted to compare neural responses to anticipation and receipt of monetary rewards in recovered patients and closely matched female healthy controls using an established paradigm.[16,32] For this analysis, we focused on the ventral striatum and medial OFC (mOFC), the 2 key regions involved in bottom–up processing of rewarding stimuli. We chose to study recovered patients to avoid confounding effects of undernutrition, which often raises the question whether findings in underweight patients with anorexia nervosa are a cause or consequence of starvation. Second, we hypothesized that individuals with anorexia nervosa inhibit (innate) drives and exert extraordinary self-control indicated by an increased recruitment of dorsal executive circuitry.[31] Therefore, we tested whether recovered patients would show increased DLPFC activity and/or coupling with the aforementioned valuation-related regions of interest (ROI) in response to anticipated and obtained monetary gains.

Methods

Participants

We recruited female patients recovered from anorexia nervosa and pairwise matched healthy female controls for participation in our study. To be considered "recovered," patients had to 1) maintain a BMI greater than 18.5 (≥ 18 yr) or greater than the tenth age percentile (< 18 yr) for at least 6 months before the study; 2) menstruate; and 3) not have binged, purged, or engaged in significant restrictive eating patterns. Anorexia was diagnosed using the expert version of a semistructured research interview: the Structured Interview for Anorexia and Bulimia Nervosa for DSM-IV (SIAB-EX).[33] Control participants had to have a healthy weight, be eumenorrhoeic and have no history of psychiatric illness. We applied several additional exclusion criteria for each group (Appendix 1, available at jpn.ca); most importantly, these were a history of bulimia nervosa or "regular" binge eating, use of psychotropic medications within 6 weeks before the study, substance abuse and neurologic or medical conditions. We carried out case–control matching using the SPSS "Fuzzy" algorithm, allowing for a maximum difference of 2 years between the individuals within 1 pair.

The Institutional Ethics Review Board of the Technische Universität Dresden, Germany, approved our study protocol, and all participants (and their guardians if the participants were underage) provided written informed consent.

Clinical measures

To complement the information obtained with the clinical interviews, we assessed eating disorder–specific psychopathology using the German version of the Eating Disorders Inventory (EDI-2[34]), depressive symptoms using the German version of the Beck Depression Inventory (BDI-II[35]) and general levels of psychopathology and anxiety symptoms using the revised Symptom Checklist 90 (SCL-90-R[36]; Appendix 1).

Instrumental motivation task

Participants performed a modified version of the common monetary incentive delay paradigm,[15] the instrumental motivation task, while lying in the MRI scanner.[16,32] In addition to allowing for measurement of event-related brain activity in response to stimuli predicting monetary reward (reward anticipation) and feedback about the magnitude of the reward received, this particular task variant has the advantage of providing behavioural assessment of motivation operationalized as instrumental responding (no. of button presses) to maximize reward.[16]

Each trial included an anticipation phase, a motor response phase and a feedback (receipt) phase (Fig. 1). The scanning

session started with an 8-trial test run to determine each individual's maximum number of button presses. This information was used to standardize the cumulative monetary gain to about €10 in the subsequent main run, irrespective of inter-individual performance differences in motor speed.

Instrumental response data analysis

We compared average number of button presses and reaction times (RT) of initial responses at each reward level between recovered patients and controls using linear mixed-effects models for the analysis of repeated measurement, treating participants as random effects. We assumed a compound symmetry covariance structure for changes of instrumental response by reward level (0, 1, 10, 100) and included group (recovered patients, control) as a factor as well as an interaction effect (slope) between group and reward level. Since the variable indicating reward level was centred (and controls were used as a reference for the factor group) the intercept in controls (and intercept + main effect of group in recovered patients) represents not instrumental responses at reward level 0, but the typical response (i.e., it correlates highly with the response rate at an average reward level).

Structural and functional image acquisition, data processing and analysis

Images were acquired between 8 and 9 am following an overnight fast using standard sequences with a 3 T whole-body MRI scanner (TRIO, Siemens) equipped with a standard head coil (Appendix 1). Functional and structural images were processed with SPM8 (www.fil.ion.ucl.ac.uk/spm) within the Nipype framework (http://nipy.sourceforge.net/nipype/[37]) following standard procedures, an artifact detection tool and DARTEL (Appendix 1).

On the single participant-level a general linear model (GLM) was fit to model the brain activation in response to increasing reward levels. We modelled all 4 reward levels of the anticipation, motor response phase and feedback phase as single events (12 regressors). Additional regressors included 6 motion parameters and 1 regressor for each motion or intensity outlier volume (Appendix 1).

Based on well-established models of the reward system[38,39] and our research question, we obtained indices of activation for the bilateral ventral striatum, bilateral mOFC and left and right DLPFC (Appendix 1). Extraction of ROI activations was performed using MarsBar and the contrast images for each

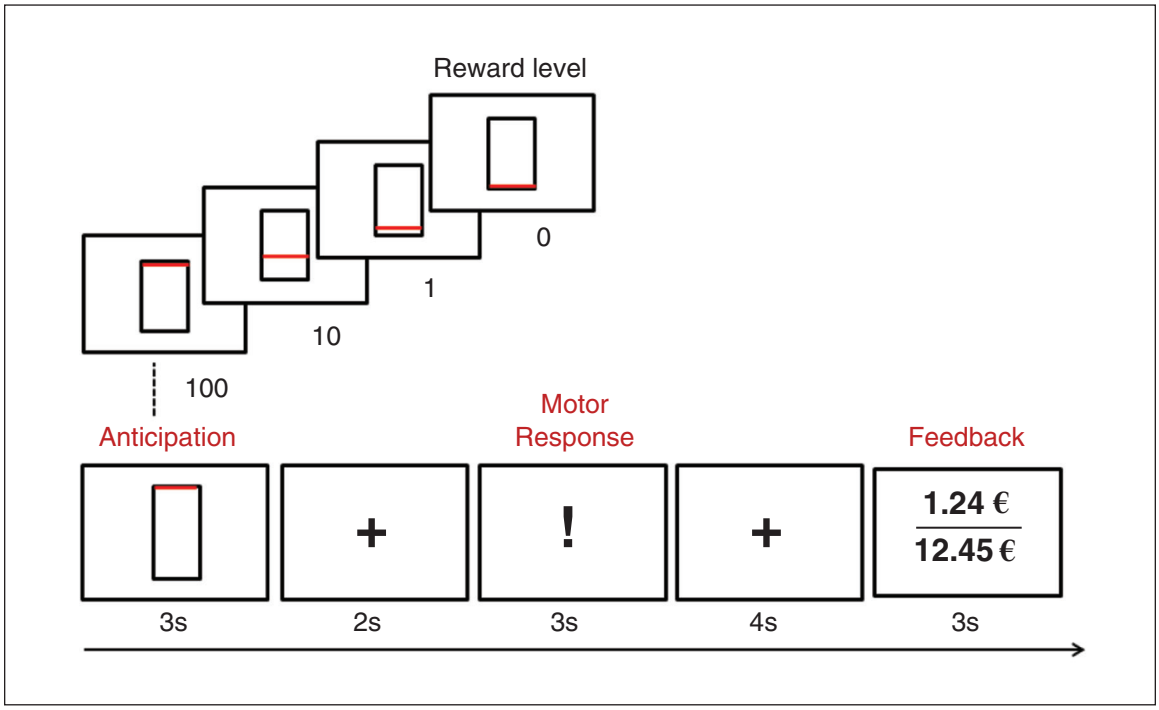

Fig. 1: Instrumental motivation task during event-related functional MRI (fMRI). During the anticipation phase a visual cue was presented for 3 s to inform the participant about the reward level of this trial (reward levels: 0 [no reward], 1, 10, 100). The motor (or instrumental) response phase started after a 2 s fixation period. Monetary reward per trial increased with reward level and higher effort and was determined by multiplying number of button presses × reward level × an individual adjustment factor (calculated based on the individual maximum no. button presses in the test run; for details see Bühler and colleagues[16]). Acoustic feedback for button presses was provided through headphones. After another fixation period of 4 s, feedback was provided for 3 s by displaying the amount of money gained in this trial and the cumulative amount. Between trials, participants fixated on crosshairs for 3 s (75%) or 7.44 s in 25% of all trials, which improves design efficiency by jittering. The fMRI main run had a total duration of 15.5 min and comprised 48 trials in total (4 reward levels × 12 pseudorandomized repetitions; Appendix 1).

reward level during anticipation and feedback obtained from the single participant–level analysis (2 × 4 contrasts). As for instrumental response data, we analyzed the extracted indices of neural responses using linear mixed models (Appendix 1). Because the phase of the menstrual cycle has been reported to modulate reward-processing,[40] we ran additional mixed-models using self-reported menstrual cycle phase as another fixed effect (Appendix 1).

In addition, whole-brain group-level analyses were performed to investigate contrasts with significant effects in the aforementioned mixed models in order to gain more insight about the exact location of the observed associations (i.e., within the DLPFC). For reward anticipation we used a single participant–level contrast weighing all reward levels equally (contrast 1), and for feedback we used a contrast modelling a parametric linear increase in brain response according to the reward level (contrast 2: –1.5, –0.5, 0.5, 1.5). To correct α error probability in second-level between-group contrast maps, we used a combination of a voxel-wise and cluster-size threshold based on results of Monte Carlo simulations using the AFNI program 3dClustSim (Appendix 1). Furthermore, we explored effects beyond our a priori–defined ROIs.

Finally, to assess functional connectivity between our aforementioned ROIs in a hypothesis-driven manner, we performed simple correlational analysis[41] using the single-participant models described previously. Time series were extracted from seed regions using the first eigenvariate adjusted for effects of interest (i.e., task and motion parameters). Seed regions were defined as spheres with a 10 mm radius centred on the most significant voxel during reward anticipation (contrast 1) from the a priori–defined ROIs (i.e., DLPFC, ventral striatum, mOFC). Based on group differences during reward anticipation, we constrained our analysis to the left DLPFC. Bivariate correlations between the left DLPFC and ventral striatum as well as between the left DLPFC and ventromedial PFC (vmPFC) were calculated for each participant, standardized using Fisher r-to-z transformation and compared using Student *t* tests.

Table 1: Demographic and clinical characteristics of the study sample

	Group, mean ± SD	
Category	Recovered patients*	Control
Age, yr	21.98 ± 3.19	21.60 ± 3.17
BMI†	21.15 ± 1.90	21.28 ± 2.16
Minimal lifetime BMI†	14.50** ± 1.84	20.02** ± 2.14
IQ‡	109.10 ± 10.41	110.96 ± 8.34
Parental SES§	3.83 ± 0.97	4.17 ± 0.87
Handedness score	0.59 ± 2.11	0.57 ± 1.87
EDI-2 total score	164.87†† ± 45.32	137.23†† ± 28.06
BDI-2 total score	8.69†† ± 8.36	4.79†† ± 5.61
SCL-90-R GSI	0.43 ± 0.39	0.34 ± 0.50
SCL-90-R anxiety	0.41 ± 0.45	0.33 ± 0.71
Age at onset, yr	14.48 ± 2.04	—
Duration of recovery, mo¶	54.83 ± 37.83	—

BDI-2 = Beck Depression Inventory, version 2; BMI = body mass index; EDI-2 = Eating Disorder Inventory, version 2; SCL-90-R GSI = revised symptom checklist 90, global symptom score; SD = standard deviation; SES = socioeconomic status.
*Twenty-three (77%) patients were of the restrictive and 7 (23%) were of the binge–purge subtype.
†BMI and minimal lifetime BMI are displayed, but statistical comparisons are based on BMI-SDS values to ensure comparability across age (Appendix 1).
‡IQ was assessed with a short version of the German adaption of the Wechsler Adult Intelligence Scale for participants aged 16 years and older or a short version of the German adaption of the Wechsler Intelligence Scale for Children for participants aged 15 years or younger (Appendix 1).
§SES ranges from 0 = leaving school without graduation to 5 = graduation from university (according to the German educational system). If the participant grew up with both parents in the same household, the estimate was based on the parent with the higher educational level.
¶Only 2 of 30 patients had a recovery time of more than 6 but less than 12 months.
**Student *t* test, $p < 0.001$.
††Student *t* test, *$p < 0.05$.

Additional statistical analyses

To test for associations between symptom scores and the magnitude of change in neural responses with increasing reward levels (using Pearson *r*), we modelled the ROI-based fMRI data in each participant using linear regression analysis. The independent variable indicating reward level was centred (i.e., the intercept represents the "typical" response). All tests were performed using SPSS version 21.0.

Results

Sample characteristics

The sample consisted of 60 female volunteers: 30 recovered patients (age 15–28 yr) and 30 controls (age 15–27 yr). There were no differences in age, BMI, IQ or handedness between the pairwise matched groups, but as expected, recovered patients had a significantly lower minimal lifetime BMI than controls. Although recovered patients were no different from controls in terms of their global psychological symptoms, they had somewhat higher eating disorder symptom scores as well as higher, but subclinical, depression scores (Table 1).

Instrumental response data

The number of button presses increased ($F_{1,180} = 182.9$, $p < 0.001$) and the RT decreased ($F_{1,180} = 156.8$, $p < 0.001$) with higher reward levels, indicating that the motivation task worked as expected (Fig. 2). We found neither a main effect of group nor an interaction between group and reward level on the number of button presses and the RT across reward levels.

Imaging data

During reward anticipation, increasing levels of monetary reward were associated with stepwise increasing neural responses in all 4 ROIs (ventral striatum: $F_{1,180} = 89.7$, $p < 0.001$; mOFC: $F_{1,180} = 26.6$, $p < 0.001$; bilateral DLPFC: $F_{1,420} = 61.5$, $p < 0.001$; effect of hemisphere, $p = 0.12$; Fig. 3). Importantly, although this activation pattern did not differ between the groups in any of the mesocorticolimbic ROIs (all $F_{1,60} < 2.4$, $p = 0.18$), a main effect of group was revealed in the bilateral DLPFC ($F_{1,60} = 4.6$, $p = 0.036$), indicating that recovered patients had increased neural responses in these 2 brain regions

(Fig. 3A and B and Appendix 1, Table S1). However, increases in neural responses with stepwise increasing reward levels were similar in both groups in all ROIs. These results remained unaffected after controlling for the phase of the menstrual cycle and excluding recovered patients who were of the binge–purge subtype (Appendix 1, Fig. S2A and B).

During reward feedback, increasing levels of monetary reward were associated with stepwise decreasing neural responses in all 4 ROIs (ventral striatum: $F_{1,180} = 14.5$, $p < 0.001$; mOFC: $F_{1,180} = 20.7$, $p < 0.001$; bilateral DLPFC: $F_{1,420} = 26.5$, $p < 0.001$; effect of hemisphere, $p = 0.17$). While no main effect of group was evident in this analysis (all $F_{1,60} < 2.1$, $p = 0.10$), a significant group × reward level interaction emerged in the bilateral DLPFC indicating steeper decreases in BOLD responses as a function of reward level in the control group ($F_{1,420} = 10.6$, $p = 0.001$; Fig. 3D and E and Appendix 1, Table S1). These results remained significant even after controlling for menstrual cycle or excluding recovered patients of the binge–purge subtype (Appendix 1, Fig. S2C and D).

Based on group differences in ROI-based analyses, we conducted supplementary analyses to evaluate between-group differences within the DLPFC and at the whole-brain level. Stimuli predicting monetary reward (contrast 1) activated a widely distributed network in all participants in the following brain regions: middle and inferior frontal gyrus, supplementary motor area, precentral gyrus, medial superior frontal gyrus, anterior cingulate and paracingulate gyrus, middle and inferior temporal gyrus, fusiform gyrus, lingual gyrus, cuneus, ventral striatum, thalamus, hippocampus, parahippocampal gyrus and cerebellum (Appendix 1, Fig. S3A and Table S2). Compared with controls, recovered patients showed increased activation in a cluster at Montreal Neurological Institute (MNI) space $x, y, z = –36, 40, 38$ in the left DLPFC (k = 243, $t = 3.41$, $p < 0.05$, family-wise error (FWE)–corrected; Fig. 3C and Appendix 1, Fig. S4A) as well as in several other brain regions, most notably in the inferior frontal gyrus, supplementary and primary motor cortex, cingulate and inferior parietal lobule (Appendix 1, Fig. S5 and Table S3).

During reward feedback (contrast 2), the right inferior parietal lobule and vermis were activated in all participants (Appendix 1, Fig. S3D and Table S4). Recovered patients had increased activation compared with controls, at MNI space $x, y, z = 14, 32, 54$ in the right DLPFC (k = 151, $t = 3.44$, $p < 0.05$, FWE-corrected; Fig. 3F and Appendix 1, Fig. S4B) but not in other regions.

Analyses of functional connectivity revealed that while no group differences in the covariation of time courses between the left DLPFC and bilateral ventral striatum were present (Appendix 1, Table S5), recovered patients had significantly higher correlations between the left DLPFC and mOFC than controls ($t_{58} = 3.530$, $p = 0.001$).

Brain–behaviour associations

We were interested in the associations between behavioural and neural responses during reward anticipation across different reward levels. Simple correlational analysis indicated stronger associations between behavioural and DLPFC activity in recovered patients than in controls (Appendix 1, Table S6). Accordingly, in linear mixed models the typical participant-specific number of button presses or RT during the anticipation of monetary reward (estimated using a centred variable indicating reward level) had a significant main effect on bilateral DLPFC activity (no. of button presses: $F_{1,67.4} = 12.0$, $p = 0.001$; RT: $F_{1,67.4} = 8.3$, $p = 0.005$). In other words,

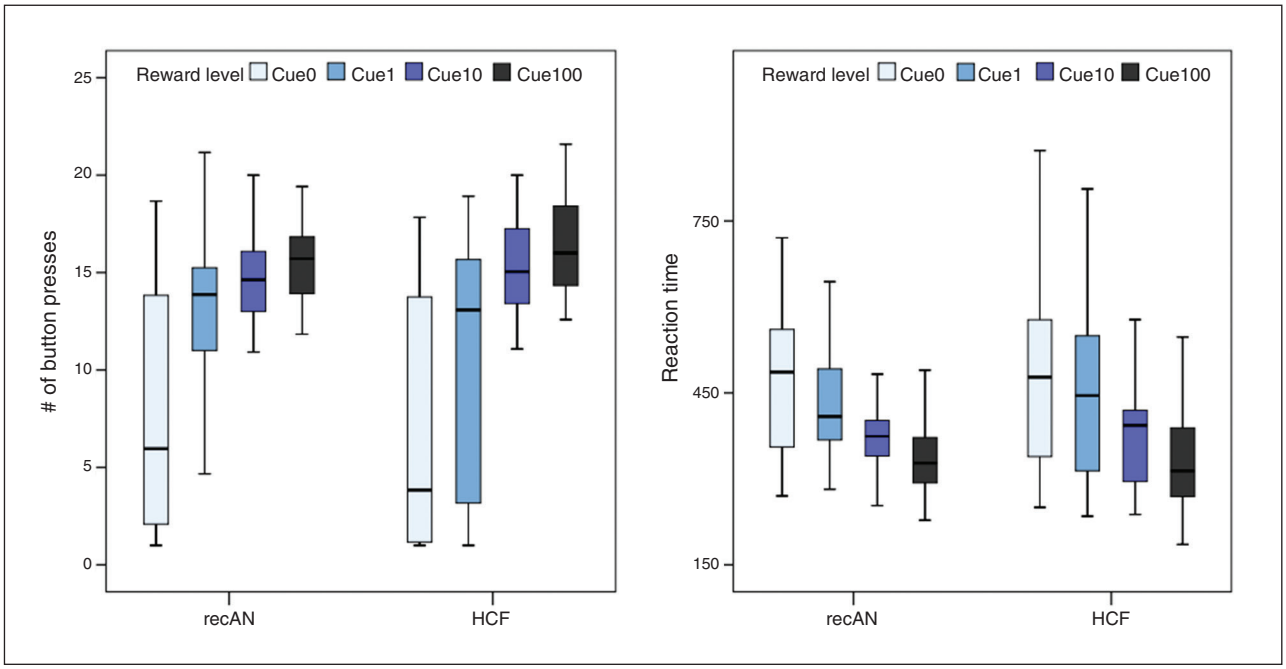

Fig. 2: Number of button presses and reaction times (RT) for each reward level ("Cue") and group during the motivation task.

higher number of button presses and faster RT were coupled with increased neural responses in these 2 brain regions at the average reward level during anticipation. This coupling of instrumental and bilateral DLPFC brain responses was stronger in recovered patients (group × behavioural response interaction for no. of button presses $F_{1,67.4} = 8.2$, $p = 0.006$ and for RT $F_{1,67.4} = 6.4$, $p = 0.014$; Appendix 1, Fig. S5).

Associations with basic demographic and eating disorder–specific clinical variables

Analyses of correlations between the pattern of hemodynamic activity in the DLPFC both during reward anticipation and in response to increasing reward during feedback showed no associations with age, BMI, minimal lifetime BMI or EDI-2 total score in either of the groups (recovered patients: all $r < 0.20$, all $p > 0.30$; controls: all $r < 0.36$, all $p > 0.05$; Appendix 1, Table S7). Similarly, functional connectivity measures (DLPFC–ventral striatum and DLPFC–mOFC) did not correlate with age, BMI, minimal lifetime BMI, or EDI-2 total score.

Discussion

In a comparatively large sample of recovered patients and closely matched controls, we found no group differences either behaviourally or in neural responses in the mesocorticolimbic system (i.e., ventral striatum and mOFC) either in anticipation of or in response to monetary rewards. However, as hypothesized, during both phases of the instrumental reward paradigm, recovered patients showed increased recruitment of the DLPFC, a brain region broadly implicated in top–down executive control.[20,21] During reward anticipation, DLPFC activity was higher in recovered patients than controls, independent of reward magnitude. During feedback, the decrease of DLPFC activity with increasing reward levels observed in controls was absent in recovered patients. Furthermore, compared with

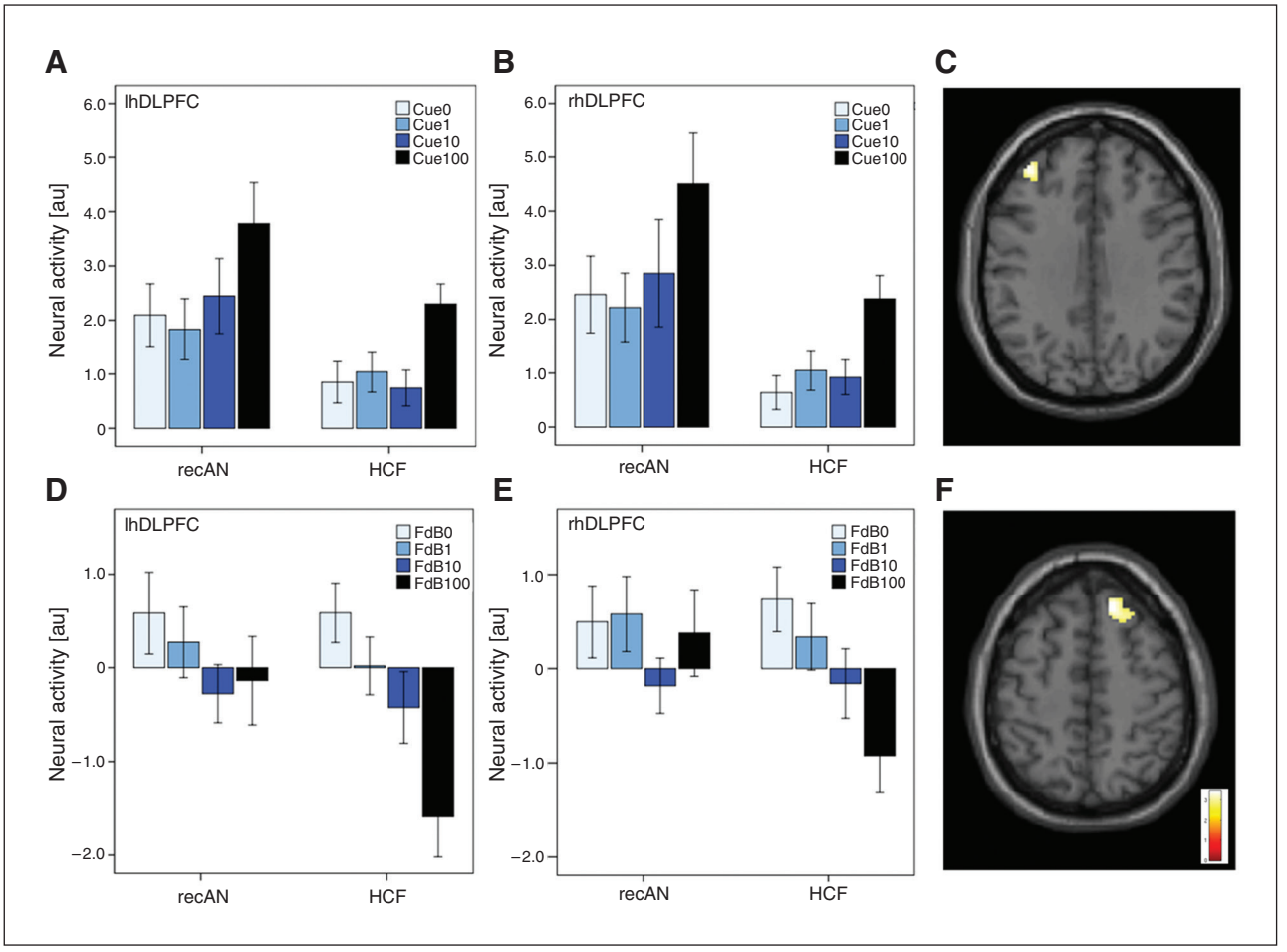

Fig. 3: Cue-related (i.e., reward anticipation, "Cue," **A–C**) and feedback-related (i.e., reward reception, "FdB," **D–F**) brain activity in response to varying monetary stimuli in the dorsolateral prefrontal cortex (DLPFC) in recovered patients (recAN) and healthy controls (HC). The first 2 columns show blood oxygen level–dependent response data of the left (lh)DLPFC (**A, D**) and right (rh)DLPFC (**B, E**) across the different reward levels (mean β ± standard error of the mean). The last columns (**C, F**) depict corresponding statistical parametric maps (i.e., contrast 1 during reward anticipation in panel **C** and contrast 2 during feedback in panel **F**) overlaid on a template T_1-weighted MRI scan (presented in neurologic convention) at a combined voxel-wise threshold of $p < 0.005$ and cluster size ≥ 135 voxels for the lhDLPFC and ≥ 141 voxels for the rhDLPFC, which corresponds to a corrected threshold of $p < 0.05$.

controls, recovered patients were characterized by stronger functional connectivity between the DLPFC and mOFC as well as stronger coupling between instrumental responses (i.e., higher no. of button presses and faster RT, and higher average DLPFC activity). Together, these findings are consistent with the hypothesis that the readily observable anhedonic and ascetic behaviours in patients with anorexia nervosa might be due to increased top–down cognitive control over motivationally salient cues.[3,31]

The literature on reward processing in patients with anorexia nervosa is somewhat contradictory. Based on self-report or behavioural data, some researchers have suggested reduced reward sensitivity in patients with anorexia nervosa,[42,43] but others have reported no group differences.[44] While an fMRI study in recovered patients[10] using a guessing game pointed to a general dysfunction of the reward system in patients with anorexia nervosa, this finding could not be verified in acutely underweight adolescents with anorexia nervosa,[45] suggesting that the abnormalities may not represent a trait effect. Using disease-relevant stimuli, such as food or thin body images, other studies have reported a hyposensitivity[17] or hypersensitivity of the brain reward system in recovered adults[12,43] and in adults[13] and adolescents[46] with acute anorexia nervosa. These diverging results might be explained by the use of different reward stimuli, differences between patients with acute anorexia nervosa and recovered patients and differences in chronicity. Taken together, results of previous studies and the present findings may suggest that there are no consistent reward processing–related group differences in the mesocorticolimbic system when comparing recovered patients and controls (at least for non–disease related reward stimuli). Given that neural processing of monetary rewards (decreased hemodynamic responses in the ventral striatum) has been shown to be impaired in patients with various neuropsychiatric disorders, such as schizophrenia,[47] substance-related disorders[16] and ADHD,[48] our finding would reflect the relatively unique psychopathology and personality characteristics of patients with anorexia nervosa, particularly the commonly high motivation to perform and compete and the surprisingly low occurrence of substance abuse.[49]

The altered response to reward anticipation and feedback in recovered patients in the present study occurred in a brain region associated with cognitive control. Recovered patients not only engaged the DLPFC to a greater extent than controls during reward anticipation, they also failed to deactivate the DLPFC after feedback about increasing amounts of monetary reward (Appendix 1). Although it can be speculated that these results merely reflect disease-related neural inefficiency[50] (i.e., compensatory mechanisms needed to achieve the same behavioural result as that observed in controls), it should be noted that our task placed no particular demands on the executive system. Two additional findings provide further support for the likelihood that the observed patterns of DLPFC activity in recovered patients in the context of our task reflect elevated cognitive control over reward-related processing. First, DLPFC activity showed significantly stronger functional coupling with the mOFC in recovered patients than in controls. Electrophysiological studies in monkeys and neuroimaging studies in healthy participants implicate the mOFC as the root of all value, namely that (primary and secondary) reinforcers are represented on a common scale of goal or subjective value that guides subsequent decision-making.[51] Although our connectivity analysis does not allow for inferences about causality, it is possible that this finding indicates increased control of valuation processes.[19] Such a possibility would be consistent with everyday clinical observation in relation to primary rewards (e.g., food, sex[4–9]) in patients with anorexia nervosa. Second, we also observed a greater association between DLPFC responses during reward anticipation and subsequent instrumental responding (no. of button presses and RT) in recovered patients than in controls. Together, these findings can be interpreted as signs of elevated cognitive control in a task that does not primarily target dorsal cognitive circuit function. Increased cognitive control of rewarding stimuli may be a trait marker of anorexia nervosa.[3,31] Individuals with these capabilities may be able to follow a diet longer and more meticulously than others. This may render them vulnerable for an onset or relapse of anorexia nervosa. Aspects of strong cognitive control mechanisms are also seen in a variety of other aspects of anorexia nervosa, such as perfectionism, cognitive inflexibility and obsessive–compulsive personality traits, which frequently precede the onset of the disorder.[4,23,52,53]

A small number of previous fMRI studies have provided some evidence suggesting that cognitive control might be elevated in patients with anorexia nervosa. The study by Wagner and colleagues[10] not only reported an absence of a differential anteroventral striatal response, but also showed an increased activation in dorsal (executive) parts of the striatum and the prefrontal and parietal cortices, which has been interpreted as the neural correlates of strategic (as opposed to hedonic) means of responding to reward. During the presentation of visual food cues (i.e., another paradigm that does not place strong demands on cognitive control), patients with acute anorexia nervosa, restrictive subtype, showed increased DLPFC activity,[28] and DLPFC activity in patients with atypical anorexia nervosa was predicted by working memory performance and the amount of obsessive–compulsive symptoms.[29] Dorsolateral PFC volume in patients with anorexia nervosa seems to be positively related to dietary restraint (i.e., cognitive strategies to inhibit appetite).[54] Furthermore, 2 studies using go/no-go task designs provide evidence suggesting altered inhibition-related neural responses in lateral frontal and parietal brain regions.[27,55] In line with the interpretation offered previously, a recent study focusing on working memory with a task that targeted the frontoparietal cognitive control network found no evidence for cortical inefficiency in patients with anorexia nervosa.[56] Taken together, these studies and our present work are consistent with the hypothesis that individuals with anorexia nervosa have increased higher-order inhibitory network function. Given that our data also indicate that mesocorticolimbic processes appear to be normal in recovered patients, one might speculate whether otherwise adequate ventral striatal circuit output is too strongly inhibited by hyperactive signalling from cognitive domains such as the DLPFC.

Limitations

Determining whether abnormalities are a consequence or a potential antecedent of pathologic eating behaviour is one of the most difficult questions in the field of eating disorder research.[57] By studying recovered patients, we attempted to exclude the effects of acute undernutrition, but abnormalities in recovered patients might still be linked more to effects of prolonged malnutrition, to compensatory effects or to the good prognosis of this particular group than to the pathogenesis of their illness. However, a strength of the present study is the unique sample, which consisted of relatively young and unmedicated recovered patients with a short duration of illness and predominantly a restrictive anorexia nervosa subtype, reducing potentially confounding effects. An alternative explanation of our findings that is also consistent with the reward-deficiency hypothesis of acute anorexia nervosa is that increased DLPFC activation in successfully recovered patients reflects a compensatory top–down upregulation (to healthy levels of functioning) of the attenuated bottom–up signal forwarded by the mesocorticolimbic system.[58] Further studies are needed to determine if recovered patients share similar neural responses with patients with acute anorexia nervosa and will help to dissociate the 2 hypotheses based on their predictions.

Conclusion

Instrumental motivation involves the integration of bottom–up reward signals represented within the mesocorticolimbic system and top–down cognitive control encoded in the DLPFC. Whereas bottom–up reward signals were similar between recovered patients and controls, recovered patients had a different pattern of activation in and connectivity with the DLPFC, which is consistent with the hypothesized exaggerated cognitive control of reward processing. Although findings from laboratory studies trying to simulate specific cognitive-affective states have to be interpreted with caution, knowledge of this neurofunctional dissociation could have important clinical implications. Much in the same way that cognitive remediation therapy addresses the inflexible and detail-focused thinking styles in patients with anorexia nervosa,[59] similar interventions could be used to become aware of and selectively reduce unnecessarily elevated cognitive control. Alternatively, TMS may be of use in very severe cases to modulate DLPFC activity.[60] In summary, improved understanding of the basic pathophysiology of anorexia nervosa offers targets for the development of better treatment strategies for this chronic and devastating disorder.

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References

1. Steinhausen HC. The outcome of anorexia nervosa in the 20th century. *Am J Psychiatry* 2002;159:1284-93.
2. Kaye WH, Fudge JL, Paulus M. New insights into symptoms and neurocircuit function of anorexia nervosa. *Nat Rev Neurosci* 2009; 10:573-84.
3. Kaye WH, Wierenga CE, Bailer UF, et al. Nothing tastes as good as skinny feels: the neurobiology of anorexia nervosa. *Trends Neurosci* 2013;36:110-20.
4. Ehrlich S, Burghardt R, Schneider N, et al. Leptin and its associations with measures of psychopathology in patients with anorexia nervosa. *J Neural Transm* 2009;116:109-15.
5. Giel KE, Friederich HC, Teufel M, et al. Attentional processing of food pictures in individuals with anorexia nervosa — an eye-tracking study. *Biol Psychiatry* 2011;69:661-7.
6. Hebebrand J, Muller TD, Holtkamp K, et al. The role of leptin in anorexia nervosa: clinical implications. *Mol Psychiatry* 2007;12:23-35.
7. Klein DA, Schebendach JE, Gershkovich M, et al. Modified sham feeding of sweet solutions in women with anorexia nervosa. *Physiol Behav* 2010;101:132-40.
8. Raboch J, Faltus F. Sexuality of women with anorexia nervosa. *Acta Psychiatr Scand* 1991;84:9-11.
9. Davis C, Woodside DB. Sensitivity to the rewarding effects of food and exercise in the eating disorders. *Compr Psychiatry* 2002;43:189-94.
10. Wagner A, Aizenstein H, Venkatraman VK, et al. Altered reward processing in women recovered from anorexia nervosa. *Am J Psychiatry* 2007;164:1842-9.
11. Wagner A, Aizenstein H, Mazurkewicz L, et al. Altered insula response to taste stimuli in individuals recovered from restricting-type anorexia nervosa. *Neuropsychopharmacology* 2008;33:513-23.
12. Cowdrey FA, Park RJ, Harmer CJ, et al. Increased neural processing of rewarding and aversive food stimuli in recovered anorexia nervosa. *Biol Psychiatry* 2011;70:736-43.
13. Fladung AK, Gron G, Grammer K, et al. A neural signature of anorexia nervosa in the ventral striatal reward system. *Am J Psychiatry* 2010;167:206-12.
14. Schultz W, Dayan P, Montague PR. A neural substrate of prediction and reward. *Science* 1997;275:1593-9.
15. Knutson B, Adams CM, Fong GW, et al. Anticipation of increasing monetary reward selectively recruits nucleus accumbens. *J Neurosci* 2001;21:RC159.
16. Bühler M, Vollstadt-Klein S, Kobiella A, et al. Nicotine dependence is characterized by disordered reward processing in a network driving motivation. *Biol Psychiatry* 2010;67:745-52.

17. Oberndorfer TA, Frank GK, Simmons AN, et al. Altered insula response to sweet taste processing after recovery from anorexia and bulimia nervosa. *Am J Psychiatry* 2013;170:1143-51.
18. Nederkoorn C, Houben K, Hofmann W, et al. Control yourself or just eat what you like? Weight gain over a year is predicted by an interactive effect of response inhibition and implicit preference for snack foods. *Health Psychol* 2010;29:389-93.
19. Hare TA, Camerer CF, Rangel A. Self-control in decision-making involves modulation of the vmPFC valuation system. *Science* 2009; 324:646-8.
20. Ridderinkhof KR, van den Wildenberg WP, Segalowitz SJ, et al. Neurocognitive mechanisms of cognitive control: the role of prefrontal cortex in action selection, response inhibition, performance monitoring, and reward-based learning. *Brain Cogn* 2004;56:129-40.
21. Miller EK, Cohen JD. An integrative theory of prefrontal cortex function. *Annu Rev Neurosci* 2001;24:167-202.
22. Camus M, Halelamien N, Plassmann H, et al. Repetitive transcranial magnetic stimulation over the right dorsolateral prefrontal cortex decreases valuations during food choices. *Eur J Neurosci* 2009; 30:1980-8.
23. Lilenfeld LR, Wonderlich S, Riso LP, et al. Eating disorders and personality: a methodological and empirical review. *Clin Psychol Rev* 2006;26:299-320.
24. Treasure J, Schmidt U. The cognitive-interpersonal maintenance model of anorexia nervosa revisited: a summary of the evidence for cognitive, socio-emotional and interpersonal predisposing and perpetuating factors. *J Eat Disord* 2013;1:13.
25. Wagner A, Barbarich-Marsteller NC, Frank GK, et al. Personality traits after recovery from eating disorders: Do subtypes differ? *Int J Eat Disord* 2006;39:276-84.
26. Oberndorfer TA, Kaye WH, Simmons AN, et al. Demand-specific alteration of medial prefrontal cortex response during an inhibition task in recovered anorexic women. *Int J Eat Disord* 2011;44:1-8.
27. Lock J, Garrett A, Beenhakker J, et al. Aberrant brain activation during a response inhibition task in adolescent eating disorder subtypes. *Am J Psychiatry* 2011;168:55-64.
28. Brooks SJ, O'Daly O, Uher R, et al. Thinking about eating food activates visual cortex with reduced bilateral cerebellar activation in females with anorexia nervosa: an fMRI study. *PLoS ONE* 2012;7:e34000.
29. Brooks SJ, Solstrand Dahlberg L, Swenne I, et al. Obsessive-compulsivity and working memory are associated with differential prefrontal cortex and insula activation in adolescents with a recent diagnosis of an eating disorder. *Psychiatry Res* 2014;224:246-53.
30. Zastrow A, Kaiser S, Stippich C, et al. Neural correlates of impaired cognitive-behavioral flexibility in anorexia nervosa. *Am J Psychiatry* 2009;166:608-16.
31. Brooks SJ, Rask-Andersen M, Benedict C, et al. A debate on current eating disorder diagnoses in light of neurobiological findings: is it time for a spectrum model? *BMC Psychiatry* 2012;12:76.
32. Kroemer NB, Guevara A, Ciocanea Teodorescu I, et al. Balancing reward and work: anticipatory brain activation in NAcc and VTA predict effort differentially. *Neuroimage* 2014;102:510-9.
33. Fichter MaNQ. SIAB. Strukturiertes Inventar für Anorektische und Bulimische Essstörungen nach DSM-IV und ICD-10. Huber, Bern. 1999.
34. Paul TT. A. Eating Disorder Inventory-2 (EDI-2). Göttingen: Hogrefe; 2005.
35. Hautzinger M, Kühner C, Keller F. BDI-II Beck-Depressions-Inventar: Pearson Assessment & Information GmbH; 2009.
36. Franke G. SCL-90-R. Symptom-Checkliste von L. R. Derogatis-Deutsche Version. Beltz Test GMBH, Göttingen. 2002.
37. Gorgolewski KJ, Storkey AJ, Bastin ME, et al. Adaptive thresholding for reliable topological inference in single subject fMRI analysis. *Front Hum Neurosci* 2012;6:245.
38. Wise RA. Dopamine, learning and motivation. *Nature Reviews* 2004;5:483-94.
39. Robbins TW, Arnsten AF. The neuropsychopharmacology of fronto-executive function: monoaminergic modulation. *Annu Rev Neurosci* 2009;32:267-87.
40. Dreher JC, Schmidt PJ, Kohn P, et al. Menstrual cycle phase modulates reward-related neural function in women. *Proc Natl Acad Sci U S A* 2007;104:2465-70.
41. Smith SM, Miller KL, Salimi-Khorshidi G, et al. Network modelling methods for FMRI. *Neuroimage* 2011;54:875-91.
42. Harrison A, O'Brien N, Lopez C, et al. Sensitivity to reward and punishment in eating disorders. *Psychiatry Res* 2010;177:1-11.
43. Watson KK, Werling DM, Zucker NL, et al. Altered social reward and attention in anorexia nervosa. *Front Psychol* 2010;1:36.
44. Jappe LM, Frank GK, Shott ME, et al. Heightened sensitivity to reward and punishment in anorexia nervosa. *Int J Eat Disord* 2011; 44:317-24.
45. Bischoff-Grethe A, McCurdy D, Grenesko-Stevens E, et al. Altered brain response to reward and punishment in adolescents with anorexia nervosa. *Psychiatry Res* 2013;214:331-40.
46. Fladung AK, Schulze UM, Scholl F, et al. Role of the ventral striatum in developing anorexia nervosa. *Transl Psychiatry* 2013;3:e315.
47. Juckel G, Schlagenhauf F, Koslowski M, et al. Dysfunction of ventral striatal reward prediction in schizophrenia. *Neuroimage* 2006; 29:409-16.
48. Scheres A, Milham MP, Knutson B, et al. Ventral striatal hyporesponsiveness during reward anticipation in attention-deficit/hyperactivity disorder. *Biol Psychiatry* 2007;61:720-4.
49. Gadalla T, Piran N. Co-occurrence of eating disorders and alcohol use disorders in women: a meta analysis. *Arch Women Ment Health* 2007;10:133-40.
50. Callicott JH, Mattay VS, Verchinski BA, et al. Complexity of prefrontal cortical dysfunction in schizophrenia: more than up or down. *Am J Psychiatry* 2003;160:2209-15.
51. Grabenhorst F, Rolls ET. Value, pleasure and choice in the ventral prefrontal cortex. *Trends Cogn Sci* 2011;15:56-67.
52. Sarrar L, Ehrlich S, Merle JV, et al. Cognitive flexibility and Agouti-related protein in adolescent patients with anorexia nervosa. *Psychoneuroendocrinology* 2011;36:1396-406.
53. Schneider N, Salbach-Andrae H, Merle JV, et al. Psychopathology in underweight and weight-recovered females with anorexia nervosa. *Eat Weight Disord* 2009;14:e205-11.
54. Brooks SJ, Barker GJ, O'Daly OG, et al. Restraint of appetite and reduced regional brain volumes in anorexia nervosa: a voxel-based morphometric study. *BMC Psychiatry* 2011;11:179.
55. Kullmann S, Giel KE, Hu X, et al. Impaired inhibitory control in anorexia nervosa elicited by physical activity stimuli. *Soc Cogn Affect Neurosci* 2014;9:917-23.
56. Lao-Kaim NP, Giampietro VP, Williams SC, et al. Functional MRI investigation of verbal working memory in adults with anorexia nervosa. *Eur Psychiatry* 2014;29:211-8.
57. Frank GK. Altered brain reward circuits in eating disorders: Chicken or egg? *Curr Psychiatry Rep* 2013;15:396.
58. Uher R, Brammer MJ, Murphy T, et al. Recovery and chronicity in anorexia nervosa: brain activity associated with differential outcomes. *Biol Psychiatry* 2003;54:934-42.
59. Brockmeyer T, Ingenerf K, Walther S, et al. Training cognitive flexibility in patients with anorexia nervosa: a pilot randomized controlled trial of cognitive remediation therapy. *Int J Eat Disord* 2014; 47:24-31.
60. Van den Eynde F, Guillaume S, Broadbent H, et al. Repetitive transcranial magnetic stimulation in anorexia nervosa: a pilot study. *Eur Psychiatry* 2013;28:98-101.