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Reward and psychopathological correlates of eating disorders: The explanatory role of leptin

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ABSTRACT

It has been hypothesized that leptin level alterations in Eating Disorders (EDs) represent a maintaining factor for pathological reward-related ED behaviors, given leptin role in the dopaminergic reward systems. The aim of the present study was to evaluate the role of leptin in EDs as a mediator for the relationship between Body Mass Index (BMI) and several pathological behaviors, such as dietary restraint, compensatory exercise, vomiting, binge eating and emotional eating. Sixty-two patients with EDs and 41 healthy controls (HC) had their blood drawn and completed psychometric tests for the evaluation of general psychopathology, ED psychopathology and emotional eating. Moderated linear regression models showed that, in the presence of high levels of ED psychopathology, leptin levels were negatively associated with dietary restraint and compensatory exercise, and positively with emotional eating and binge eating. Finally, leptin showed an indirect effect on the association between BMI and all these reward-related behaviors. These results suggest that a variation of BMI maintains these pathological ED behaviors through a variation in leptin levels. Considering the role of leptin in reward circuits, the results seem to confirm an aberrant food-related reward mechanism in ED patients.

1. Introduction

Eating Disorders (EDs) are complex psychiatric disorders characterized by a common psychopathological core represented by an excessive importance attributed to body shape and weight (American Psychiatric Association, 2013). The development and maintenance of these disorders involve sociocultural, psychological and biological factors (Striegel-Moore and Cachelin, 2001). In particular, alterations of brain reward mechanisms seem to have a role in maintaining EDs (Monteleone et al., 2018; Monteleone and Maj, 2013). Indeed, pathological eating behaviors such as dietary restraint, compensatory physical activity, emotional eating, binge eating and self-induced vomiting have been linked to reward in these patients (Meye and Adan, 2014; Monteleone et al., 2018; Monteleone and Maj, 2013; Pearson et al., 2015). Dopaminergic dysfunctions in these patients could be induced by malnutrition, both in terms of underweight and overweight, because of the imbalance of molecules that regulate hunger and satiety. These do not only have a homeostatic role in appetite regulation, but also act in brain areas that are involved in the hedonic regulation of food intake (Monteleone and Maj, 2013). Among these substances, one of the most studied is leptin, an adipokine produced by adipocytes whose circulating levels positively correlate with adipose tissue size (Brennan and Mantzoros, 2006) and Body Mass Index (BMI) (Monti et al., 2006). Leptin levels have been described to be reduced in Anorexia Nervosa (AN) (Hebebrand et al., 1997; Karageorgiou et al., 2019) and increased in Binge-Eating Disorder (BED) (Monteleone et al., 2000b), with conflicting results in Bulimia Nervosa (BN) (Ferron et al., 1997; Jimerson et al., 2000; Monteleone et al., 2000b). The main function of leptin is informing the central nervous system on the amount of energy stores, thus regulating energy balance by inducing a sensation of satiety through the stimulation of the arcuate nucleus of the hypothalamus (Brennan and Mantzoros, 2006). Moreover, it has been demonstrated that leptin, other than having the aforementioned homeostatic function, is also involved in the suppression of food-related

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reward via its action on Ventral Tegmental Area (VTA) (Leinninger et al., 2009). Thus, it has been argued that leptin level modifications in EDs are not just a consequence of malnutrition, but they also represent a mechanism of maintenance of pathological reward-related eating behaviors (Monteleone and Maj, 2013).

This hypothesis is supported by clinical and experimental studies. Von Prittwitz et al. (1997) demonstrated, in a population of underweight girls, a correlation between low leptin levels and restrained eating, independently from body fat mass. Moreover, it has been demonstrated that low leptin levels resulted associated with excessive physical activity, both in patients with AN (Holtkamp et al., 2006) and in animal models (de Rijke et al., 2005). In the latter, the administration of leptin in the VTA inhibited this behavior (Verhagen et al., 2011). With regard to binge eating and self-induced vomiting, a negative correlation with leptin levels was reported by Monteleone in a sample of patients affected by BN (Monteleone, 2002), whereas Jimerson et al. (2000) confirmed the negative relationship with binge episodes, but did not find any significant correlation with the frequency of self-induced vomiting. On the contrary, studies performed in patients affected by BED reported a positive relationship between leptin levels and binge episodes (Adami et al., 2002; Miller et al., 2014; Monteleone et al., 2000b). Finally, Michels et al. (2017) reported that leptin positively moderated the relationship between stress and emotional eating in a female children population. The available studies, however, showed some limitations, such as being based on non-clinical or mixed populations (Michels et al., 2017; von Prittwitz et al., 1997), considering children cohorts (Michels et al., 2017), or reporting conflicting results (Adami et al., 2002; Jimerson et al., 2000; Monteleone, 2002; Monteleone et al., 2000b). To the best of our knowledge, leptin has never been included in an explanatory model of maintenance of EDs in a population of patients with AN, BN and BED, evaluating its role as a mediator in the relationship between malnutrition and psychopathological and behavioral correlates of EDs. Considering the inhibitory role of leptin on dopaminergic circuits, we hypothesized that low leptin levels in ED patients could maintain pathological reward-related eating behaviors associated with low body weight, including food restriction, compensatory exercise, and self-induced vomiting. Additionally, given that a reduced dopaminergic tone has been implicated in the maintenance of addictions and craving (Volkow et al., 2011), we suggest that high leptin levels could maintain pathological eating behaviors related to an elevated BMI, such as binge eating and emotional eating, which have been linked to addictions and craving (Leslie et al., 2018; Penaforte et al., 2019).

On the basis of the above considerations, the aims of the present study were as follows: (1) to evaluate the relationship between leptin and psychopathological correlates of EDs in a clinical setting of patients with AN, BN and BED; (2) to elucidate the role of leptin levels in the maintenance of EDs, integrating it as a mediator of the relationship between BMI and specific reward-related behaviors, including dietary restraint, compensatory exercise, self-induced vomiting, objective binge eating and emotional eating.

2. Methods

A cross-sectional observational study was conducted at the Day Hospital service of the Psychiatric Unit of the University of Florence, Italy. Patients were referred by their general practitioner or other clinicians. All diagnostic procedures were performed in the context of the routine initial evaluation.

2.1. Ethical statement

Patients were adequately informed about the study and signed a consent form. The study protocol was approved by the ethics committee of the local Institution (Ethical Committee Area Vasta Centro, reference number OSS.14.162).

2.2. Participants

Patients were enrolled between November 2017 and May 2019, provided they met the following inclusion criteria: female sex, age between 18 and 60 years, current diagnosis of AN, BN or BED according to DSM-5 criteria (American Psychiatric Association, 2013). Exclusion criteria were as follows: comorbid schizophrenia, bipolar I disorder, acute psychotic disorder, illiteracy, intellectual disability, severe medical comorbidities, such as severe heart/renal/liver diseases, current use of psychoactive medications, with the exception of antidepressants (ADs) and benzodiazepines. Of the 74 ED patients referred, 5 subjects declined to participate and 7 were excluded (1 bipolar disorder, 3 severe medical conditions, 3 use of antipsychotic or mood stabilizers).

Healthy controls (HC) were recruited by means of local advertisements among students of this University, provided they met the following inclusion criteria: female sex, age between 18 and 60, absence of any mental disorder as assessed by a clinical evaluation and BMI between 18.5 and 25.0 kg/m^2.

2.3. Assessment and measures

During the initial evaluation, which was performed by two expert psychiatrists (G.C. and V.R.), sociodemographic, pharmacological and clinical data were collected through a face-to-face interview, along with information on the frequency of binge-eating episodes, compensatory exercise and self-induced vomiting in the previous month. Standard calibrated instruments were used in order to collect anthropometric measurements (weight and height). The BMI was calculated with the following formula: body weight in kilograms divided by height in meters squared. Serum blood samples were drawn at 8:00 A.M. after a night of fasting. Both patients and HCs followed the same study procedures.

Serum leptin was measured with Huma Leptin SimpleStep ELISA® (Enzyme-Linked Immunosorbent Assay) kit (Abcam, Cambridge, UK), in accordance with manufacturer's instructions.

In order to evaluate general and specific ED psychopathology the following questionnaires were administered to all participants:

2.3.1. Symptom Checklist-90 revised (SCL-90-R)

A self-report questionnaire that evaluates general psychopathology through 90 items, with a score from “not at all” (0) to “extremely” (4) (Derogatis et al., 1973). It provides a global severity index (GSI), which is the average of the scores reported in all the items.

2.3.2. Eating Disorder Examination Questionnaire version 6.0 (EDE-Q 6.0)

A self-administered questionnaire that assesses the behavioral and cognitive features of EDs (Fairburn, 2008). The respective subscales are obtained from the average of specific items related to restraint, eating concern, weight concern and shape concern A total score can be calculated by averaging the scores of the four subscales.

2.3.3. Emotional Eating Scale (EES)

A 25-item questionnaire that assesses the urge to eat resulting from specific moods or negative emotions, ranging between 0 (no desire to eat) and 4 (very strong desire to eat) (Arnow et al., 1995). Its 3 subscales evaluate the desire to eat in relation to emotions belonging to the domains of anger, anxiety, and depression. The total score is obtained from the sum of all the items.

2.4. Statistical analyses

Continuous variables were reported as mean ± standard deviation (SD). Univariate comparisons between groups were performed by means of independent samples *t*-tests or Analysis of Variance (ANOVA) with Tukey post-hoc analysis. Analysis of Covariance (ANCOVA) was used for age and BMI-adjusted comparisons, post-hoc analyses were

performed with a Bonferroni adjustment. Two pairs of groups were compared: patients vs. HCs and bingeing vs. non-bingeing patients. The latter comparison was carried out in light of the high rate of diagnostic crossover found in subjects suffering from EDs (Castellini et al., 2018, 2011), in order to study the behaviors of patients rather than the diagnosis itself. Associations between variables were tested by means of Pearson correlation coefficient. Furthermore, leptin level correlates were tested in a multivariate linear regression analysis, adding age and BMI as covariates.

The main aim of the present study was to verify whether leptin was involved in the maintenance of reward-related pathological behaviors: to test this hypothesis, moderation analyses were performed for the association between leptin and the outcome variables, with ED-specific psychopathology as a moderator variable. This was achieved by linear regression analyses, entering leptin levels, EDE-Q, and the Leptin*EDE-Q interaction as independent variables. In the model on food restriction, given that the pathological behavior was measured by an EDE-Q subscale, the "EDE-Q Weight Concern" variable was inserted as the moderating variable rather than the total score in order to avoid multicollinearity problems. In the aforementioned models, outcome variables were: monthly episodes of objective binge eating, emotional eating (as measured by “EES Total Score”), food restriction (as measured by “EDE-Q Restraint”), monthly episodes of compensatory exercise, and self-induced vomiting. Furthermore, leptin levels were regressed as an indirect effect between BMI and the aforementioned reward-related behaviors, adopting ED psychopathology as a moderator of this interaction.

Considering that leptin levels can also be consequent to weight variations, the inverse models were also tested, considering the indirect effect of BMI in the interaction between pathological eating behaviors (independent variable) and leptin levels. All models were run with age as a covariate.

Percentile bootstrapping with 20,000 resamples and 95% confidence intervals was used, in order to test the statistical significance of indirect effects. All moderations were tested by calculating the interaction effect and the conditional effects of the predictor on the dependent variable at different values of the moderator: one standard deviation below the mean, at the mean value, and one standard deviation above the mean. If the above values were found to be outside the range of possible values for that scale, the minimum or maximum values of the scale were used instead to probe the effects. The Johnson-Neyman technique was applied in order to calculate the transition point for statistical significance.

All analyses were performed using IBM SPSS Statistics version 25 (IBM Corp., 2017) and the PROCESS macro v.3.3 (Hayes, 2013).

3. Results

3.1. General characteristics of the sample

The final sample consisted of 41 healthy subjects and 62 patients, of which 34 fulfilled a diagnosis of AN, 14 of BN and 14 of BED. Table 1 shows the main demographic and clinical characteristics of the sample, together with the results of comparisons between groups, carried out between patients and HCs and between patients with and without bingeing behaviors. Patients reported significantly higher scores than the control group in almost all the administered questionnaires, with the exception of EES Depression.

Patients had significantly lower leptin blood levels when compared to healthy subjects in age- and BMI-adjusted multivariate comparisons (Table 1). When considering different ED diagnoses, subjects with AN showed mean leptin values of 0.4 ng/ml (SD = 0.4 ng/ml), BN of 1.3 ng/ml (SD = 1.1 ng/ml) and BED of 3.8 ng/ml (SD = 1.6 ng/ml). The ANOVA performed for differences between diagnoses was statistically significant ($F = 34.11$, $p < 0.001$), and Tukey post-hoc analysis revealed that subjects with AN and BN displayed lower leptin levels than subjects with BED and HCs, whereas subjects with BED had higher values compared to the other groups. The age- and BMI-adjusted ANCOVA performed with diagnosis as categorical fixed factor was statistically significant ($F = 6.55$, $p = 0.001$), and Bonferroni-adjusted post-hoc tests revealed lower leptin levels for AN (mean difference = −1.3 ng/ml, $p = 0.001$) and BN (mean difference = −1.1 ng/ml, $p = 0.02$), as compared to healthy subjects.

As expected, patients exhibiting bingeing behaviors showed higher BMI when compared to restrictive patients, with an earlier onset of the ED, a longer duration of illness and a greater number of overeating, binge-eating and self-induced vomiting episodes (Table 1). Overall, bingeing patients reported higher scores in administered questionnaires, with only the anger related EES subscale not showing a significant difference (Table 1). When considering leptin, no significant differences were found when adding age and BMI in the multivariate analysis (Table 1).

3.2. Clinical and psychopathological correlates of leptin

As expected, BMI significantly predicted leptin levels in both healthy HCs and patients, even when adjusting for age ($\beta = 0.67$, $p < 0.001$ and $\beta = 0.91$, $p < 0.001$, respectively).

Table 2 reports a correlation matrix for the psychometric and clinical variables under study. Pearson correlation analyses in patients showed a positive association between blood levels of leptin and EDE-Q Weight and Shape Concern, overeating episodes, objective binge eating and emotional eating, while a negative association was present with compensatory exercise (Table 2). No association between leptin levels and any of the psychopathological variables under consideration was found in the control group.

A series of multivariate linear regression analyses were run in order to study the psychopathological correlates of leptin levels, using age and BMI as covariates; the results for the group of patients are reported in Table 3. A significant positive association was found between leptin hematic levels and each dimension of emotional eating assessed. Moreover, leptin levels were associated with the number of overeating and objective binge-eating episodes reported by patients in the last 28 days before the assessment. Conversely, no association was found with subjective binge-eating episodes and overeating without loss of control. Finally, there was an association between low leptin levels and a higher number of episodes of intense physical exercise with compensatory purposes.

No statistically significant association was observed between leptin levels and any of the measured psychopathological domains in HCs (data not reported).

To further corroborate the role of leptin in the maintaining model of pathological eating behaviors, linear regression models were carried out including leptin*ED-specific psychopathology as a covariate. This strategy was adopted to test whether leptin association with pathological behaviors (restraint, compensatory exercise, binge eating, and emotional eating) was conditioned according to different levels of core psychopathology (EDE-Q total score, weight concern). Fig. 1 reports the significant interactions. Leptin*EDE-Q Weight Concern interaction was significantly associated with the dietary restraint ($\beta = -0.40$, $p = 0.013$), indicating a different association between leptin levels and this aberrant eating behavior for different levels of ED-specific psychopathology (Fig. 1A). The association was found to be statistically significant only for higher levels of ED psychopathology (Fig. 1A): the transition point of the moderator for statistical significance was found to be 2.48. Similar results were found for physical compensatory exercise, with a significant Leptin*EDE-Q Total Score interaction effect ($\beta = -0.61$, $p = 0.001$) (Fig. 1B). The moderator value defining the region of statistical significance was 0.99.

With regard to behaviors related to overeating, linear regression models showed statistically significant Leptin*EDE-Q TS interactions for both objective binge-eating ($\beta = 0.47$, $p = 0.032$) and emotional

Table 1
Demographic and clinical characteristics of the sample, together with the results of comparisons between groups (healthy subjects vs patients and restricting vs bingeing patients), performed by independent samples *t*-tests for age and BMI, and age- and BMI-adjusted ANCOVAs for all other measures. *t* and *F*-values are shown alongside their statistical significance (* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$).

	Healthy Subjects (n = 41) Mean ± SD	Patients (n = 62) Mean ± SD	t/Age and BMI-adjusted F	Restricting Patients (n = 26) Mean ± SD	Bingeing Patients (n = 36) Mean ± SD	t/Age and BMI-adjusted F
Age (years)	25 ± 3	28 ± 12	−1.46	25 ± 11	29 ± 12	−1.45
Education (years)	14 ± 2	12 ± 3	23.32***	12 ± 3	12 ± 3	0.01
BMI (kg/m^2)	21.0 ± 2.0	21.3 ± 7.7	−0.35	16.0 ± 1.4	24.0 ± 8.0	−5.85***
Age of onset (years)		18 ± 7		21 ± 7	17 ± 7	16.81***
Illness duration (years)		9 ± 11		4 ± 9	11 ± 11	11.28**
Leptin (ng/ml)	2.3 ± 1.4	1.4 ± 1.7	14.86***	0.4 ± 0.3	2.0 ± 1.8	0.84
EDE-Q Dietary Restraint	0.7 ± 1.0	2.8 ± 2.2	33.43***	2.3 ± 2.5	3.0 ± 2.0	4.98*
EDE-Q Eating Concern	0.4 ± 0.7	2.8 ± 1.7	71.64***	1.9 ± 1.6	3.2 ± 1.6	7.42**
EDE-Q Weight Concern	1.1 ± 1.1	3.4 ± 1.8	54.90***	2.2 ± 1.7	3.9 ± 1.6	9.31**
EDE-Q Shape Concern	1.3 ± 1.3	3.6 ± 2.1	45.76***	2.5 ± 2.2	4.1 ± 1.7	6.57*
EDE-Q Total score	0.9 ± 0.9	3.1 ± 1.8	57.82***	2.2 ± 1.9	3.6 ± 1.5	8.24**
Total overeating episodes	0.7 ± 1.7	6.0 ± 9.7	10.19**	0.0 ± 0.0	8.6 ± 10.3	14.26***
Objective binge-eating episodes	0.4 ± 1.5	5.1 ± 9.0	8.97**	0.0 ± 0.0	7.4 ± 9.8	10.12**
Overeating episodes without loss of control	0.3 ± 0.7	1.0 ± 4.0	1.42	0.0 ± 0.0	1.3 ± 4.6	2.92
Subjective binge-eating episodes	0.6 ± 1.7	4.1 ± 10.3	5.25*	1.6 ± 5.0	4.9 ± 11.4	2.40
Self-induced vomiting	0.0 ± 0.0	2.7 ± 6.8	4.82*	0.0 ± 0.0	3.6 ± 7.7	5.67*
Laxatives	0.0 ± 0.0	1.9 ± 7.2	3.27	0.0 ± 0.0	2.6 ± 8.3	0.30
Diuretics	0.0 ± 0.0	1.5 ± 6.8	2.23	0.0 ± 0.0	2.1 ± 7.9	0.07
Compensatory exercise episodes	0.4 ± 2.3	8.3 ± 12.1	16.24***	13.8 ± 14.0	6.3 ± 10.4	1.75
EES Anger	6.6 ± 7.2	13.0 ± 13.5	5.34*	6.4 ± 8.5	16.6 ± 13.9	3.68
EES Anxiety	5.9 ± 5.8	10.4 ± 9.6	5.71*	5.8 ± 6.4	12.9 ± 9.7	4.21*
EES Depression	5.9 ± 4.1	6.7 ± 5.8	0.13	3.2 ± 3.7	8.8 ± 5.8	8.27**
EES Total score	18.4 ± 15.9	30.1 ± 28.0	4.05*	15.4 ± 18.4	38.3 ± 28.1	5.03*
SCL-90-R GSI	0.5 ± 0.5	1.4 ± 0.8	47.49***	1.0 ± 0.7	1.6 ± 0.7	7.09*

BMI: Body Mass Index; EDE-Q: Eating Disorder Examination Questionnaire; EES: Emotional Eating Scale; SCL-90-R GSI: Symptom Checklist-90 Revised Global Severity Index; SD: Standard Deviation.

eating ($\beta = 0.60$, $p = 0.007$). These behaviors were associated with leptin blood levels only for high ED psychopathology scores (EDE-Q Total Score higher than 1.80 and 1.85, respectively). Interaction probing is reported in Fig. 1, panels C and D. Finally, self-induced vomiting episodes were associated only with ED-specific psychopathology ($\beta = 0.61, p < 0.001$), with a non-significant Leptin*EDE-Q Total Score interaction effect ($\beta = -0.44$, $p = 0.061$).

3.3. Explicative mechanisms of the relationship between leptin and ED pathological behaviors

A significant indirect effect between BMI and EDE-Q Dietary Restraint through leptin levels was found, albeit only for higher levels of EDE-Q Weight Concern ($b = -0.10$, 95% CI: -0.21 – -0.02), despite the absence of an association between these two variables in the whole sample ($\beta = -0.13$, $p = 0.216$). The indirect association between low BMI and pathological exercise through a reduction in hematic leptin levels was statistically significant, but only in the presence of medium (indirect effect: $b = -0.71$, 95% CI: -1.20 – -0.35) or high EDE-Q Total Scores (indirect effect: $b = -1.18$, 95% CI: -1.93 – -0.61). The relationship between BMI and objective binge-eating episodes also appeared to have and indirect effect through leptin values, for medium (indirect effect: $b = 0.42$, 95% CI: 0.07 – 0.85) or high EDE-Q Total Score values (indirect effect: $b = 0.70$, 95% CI: 0.16 – 1.40.

The model concerning the association between BMI and emotional eating symptomatology indicated the presence of an indirect effect by leptin levels (indirect effect for medium EDE-Q Total Scores: $b = 1.30$, 95% CI: 0.31 – 2.58; indirect effect for high EDE-Q Total Scores: $b = 2.39$, 95% CI: 0.83 – 4.53). No significant indirect effect was found at any level of EDE-Q Total Score for the association between BMI and self-induced vomiting. All the Variance Inflation Factors (VIFs) calculated for each of the models tested were less than 3.0.

Finally, analyses were carried out to verify whether the relationship between pathological eating behaviors and leptin levels could have an indirect effect through BMI. None of these reverse models revealed a statistically significant indirect effect, with the exception of compensatory exercise (indirect effect: $b = -0.04$, 95% CI: -0.06 – -0.02).

4. Discussion

To the best of our knowledge, this is the first study which attempted to integrate leptin levels in an explanatory model of maintenance of ED psychopathology, evaluating their role in the relationship between malnutrition and aberrant reward-related behaviors.

As expected, leptin concentration was found to have a strong association with BMI, both in patients and HCs. Comparison with healthy subjects showed reduced leptin levels in AN and BN patients, and increased in those with BED, in accordance with previous findings (Brewerton et al., 2000; Hebebrand et al., 1997; Jimerson et al., 2000; Karageorgiou et al., 2019; Monteleone, 2002; Monteleone et al., 2002, 2000b, 2000a).

4.1. Reduced leptin levels and psychopathology

Leptin levels were found to be reduced in both AN and BN, even after BMI adjustment. In agreement with this result, lower leptin levels have already been observed in patients with AN as compared to HCs matched by age and BMI and/or body fat mass (Hebebrand et al., 1997), and in BN patients despite their normal weight status (Monteleone, 2002; Monteleone et al., 2000b), thus suggesting a relationship with psychopathology and pathological behaviors, relatively independent from BMI. This hypothesis appears to be supported by previous studies. In particular, von Prittwitz et al. (1997) demonstrated

Table 2
Correlation matrix for the psychometric and clinical variables under study in ED patients. The table reports all Pearson correlation coefficients, alongside their statistical significance (* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$).

	Lep	EDE-Q-R	EDE-Q-E	EDE-Q-W	EDE-Q-S	EDE-Q-TS	Tot. Ov.	OBE	Ov.	SBE	Vomit	Lax	Diur	Exer	EES-A	EES-axe	EES-D	EES-TS	SCL-GSI	BMI
Lep	–																			
EDE-Q R	−0.17	–																		
EDE-Q E	0.11	0.62***	–																	
EDE-Q W	0.27*	0.67***	0.82***	–																
EDE-Q S	0.26*	0.72***	0.81***	0.94***	–															
EDE-Q TS	0.11	0.84***	0.88***	0.94***	0.96***	–														
Tot. Ov.	0.26*	−0.01	0.36**	0.31*	0.32*	0.26	–													
OBE	0.29*	−0.05	0.38**	0.29*	0.26*	0.23	0.91***	–												
Ov.	−0.06	0.08	0.03	0.11	0.18	0.11	0.39**	−0.02	–											
SBE	−0.10	0.17	0.17	0.24	0.22	0.22	0.08	0.07	0.03	–										
Vomit	−0.14	0.29*	0.28*	0.28*	0.25	0.30*	0.29*	0.32*	−0.02	0.03	–									
Lax	−0.08	0.05	0.23	0.29*	0.27*	0.22	0.11	0.09	0.07	−0.02	0.36**	–								
Diur	−0.08	−0.03	0.22	0.29*	0.23	0.19	0.13	0.16	−0.04	0.05	0.27*	0.80***	–							
Exer	−0.50***	0.29*	0.15	0.11	0.14	0.20	−0.19	−0.14	−0.17	−0.16	−0.07	0.14	0.25	–						
EES A	0.33*	−0.04	0.45***	0.30*	0.28*	0.25	0.62***	0.71***	−0.09	−0.04	0.32*	0.14	0.22	−0.15	–					
EES axe	0.35*	0.02	0.49***	0.34**	0.32*	0.30*	0.65***	0.73***	−0.07	0.01	0.34*	0.16	0.27	−0.21	0.93***	–				
EES D	0.32*	−0.01	0.42**	0.35**	0.31*	0.28*	0.59***	0.68***	−0.06	−0.01	0.35**	0.15	0.17	−0.15	0.86***	0.8***	–			
EES TS	0.35*	−0.02	0.47***	0.33*	0.31*	0.28*	0.65***	0.74***	−0.08	−0.02	0.34*	0.15	0.23	−0.18	0.98***	0.97***	0.93***	–		
SCL-GSI	0.02	0.50**	0.71***	0.67***	0.66***	0.69***	0.26*	0.28*	0.02	0.14	0.29*	0.23	0.19	0.06	0.24	0.30*	0.31*	0.28*	–	
BMI	0.84***	−0.18	0.19	0.28*	0.27*	0.14	0.10	0.14	−0.05	−0.04	−0.06	0.26	0.27*	−0.25	0.32*	0.27*	0.27*	0.31*	0.11	–

Lep: Leptin; EDE-Q: Eating Disorder Examination Questionnaire; R: dietary restraint; E: eating concerns; W: weight concerns; S: shape concerns; TS: Total Score; Tot. Ov.: total overeating episodes; OBE: Objective Binge-Eating episodes; Ov.: Overeating episodes without loss of control; SBE: Subjective Binge-Eating episodes; Vomit: self-induced vomiting; Lax: Laxatives; Diur: Diuretics; Exer: compensatory exercise episodes; EES: Emotional Eating Scale; A: Anger; axe: Anxiety; D: Depression; SCL-GSI: Symptom Checklist-90 Revised Global Severity Index; BMI: Body Mass Index.

Table 3
Psychopathological and behavioral correlates of leptin levels in ED patients. For every dependent variable, a linear regression model was performed, with age, BMI, and leptin values as independent factors. β values are shown alongside their statistical significance (* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$).

Dependent variable	Age- and BMI-adjusted β
EDE-Q Dietary Restraint	−0.04
EDE-Q Eating Concern	0.06
EDE-Q Weight Concern	0.34
EDE-Q Shape Concern	0.32
EDE-Q Total score	0.19
Total overeating episodes	0.78**
Objective binge-eating episodes	0.83**
Overeating episodes without loss of control	−0.01
Subjective binge-eating episodes	−0.22
Self-induced vomiting	0.01
Laxatives	−0.01
Diuretics	0.19
Compensatory exercise episodes	−0.56*
EES Anger	0.59*
EES Anxiety	0.81**
EES Depression	0.61*
EES Total score	0.69*
SCL-90-R GSI	0.02

BMI: Body Mass Index; EDE-Q: Eating Disorder Examination Questionnaire; EES: Emotional Eating Scale; SCL-90-R GSI: Symptom Checklist-90 Revised Global Severity Index.

that both BMI and food restriction were independent predictors of reduced blood leptin levels.

In addition, the present study suggests that the BMI-dependent decrease of leptin levels may represent a maintaining factor for pathological ED related behaviors, as previously hypothesized by Monteleone and Maj (2013). Leptin was found to be a mediator for the relationship between reduced BMI and increased dietary restraint, and between reduced BMI and compensatory physical activity in the presence of high levels of ED specific psychopathology. These results suggest that underweight is associated with maintaining of restraint and compensatory exercise through a decrease in plasma leptin levels in subjects with severe ED psychopathology. Conceptually, the proposed analysis integrates the role of leptin into Fairburn's cognitive-behavioral model, according to which malnutrition represents a maintaining factor for pathological eating behaviors and for the psychopathological nucleus of EDs represented by the excessive importance attributed to body shape and weight (Fairburn, 2008). The results on physical activity are apparently in line with the model of semi-starvation induced hyperactivity (SIH), according to which a prolonged fasting regime favors the increase of motor activity and restlessness via a reduction of leptin levels (Exner et al., 2000). It has been hypothesized that SIH could be an adaptive consequence of prolonged fasting, with hypoleptinemia prompting the search for food through an increase in exploratory behavior (Buyse et al., 2001). This could be driven by the increase in the dopaminergic tone of the reward circuits due to low leptin levels (Verhagen et al., 2011). However, in the present study the increase in

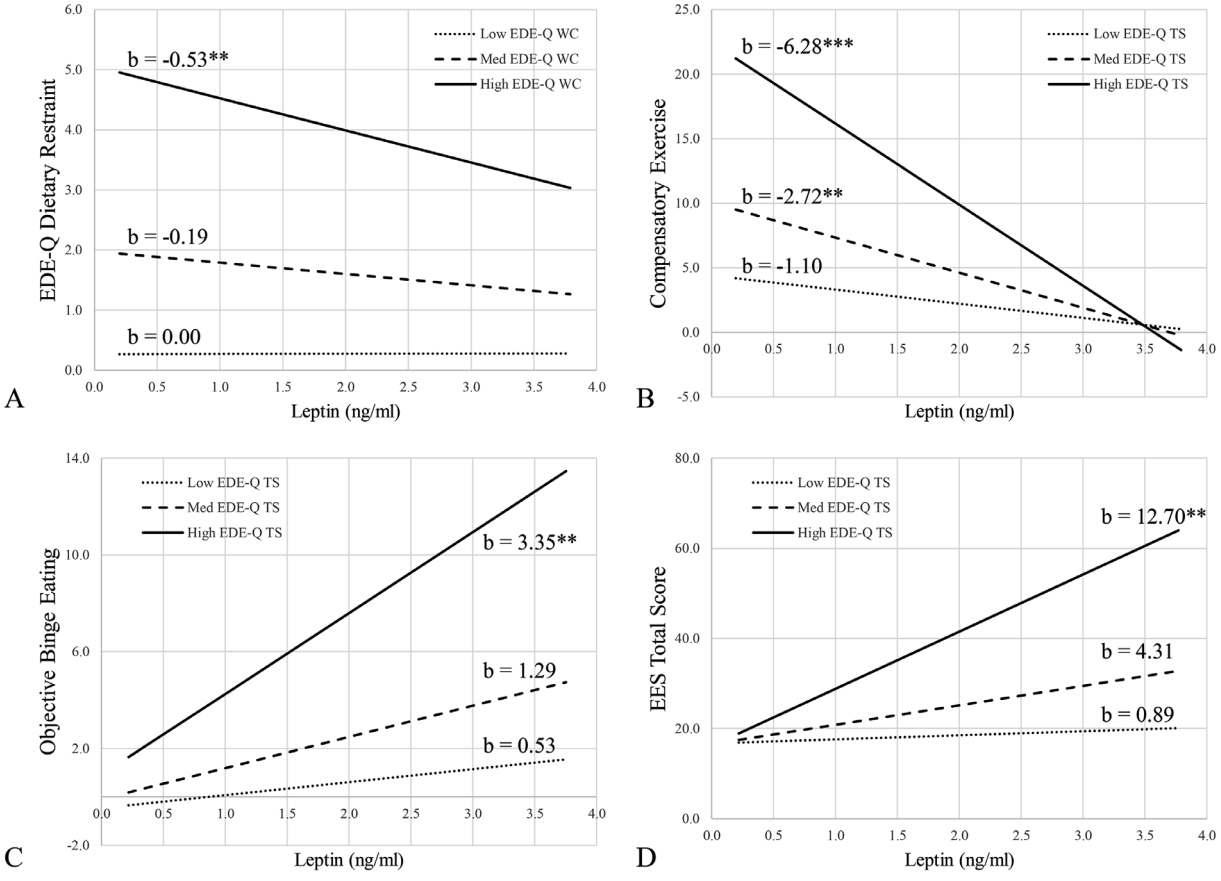

Fig. 1. Diagrams of the moderated linear regression models for dietary restraint (Panel A), compensatory physical exercise (Panel B), objective binge eating (Panel C) and emotional eating (Panel D). All models have leptin levels as the independent variable, the pathological behavior as the dependent variable, and age and BMI as covariates (not shown in the model). Eating disorder specific psychopathology was inserted as a moderator for the association between leptin values and pathological behaviors. Each panel shows the regression lines and coefficients (*b*) for the relationships between leptin and the reward-related behavior, for three different values of the moderator (a standard deviation below the mean, at the mean and a standard deviation above the mean).
** $p < 0.01$; *** $p < 0.001$
BMI: Body Mass Index; EDE-Q: Eating Disorder Examination Questionnaire; EES: Emotional Eating Scale; TS: Total Score; WC: Weight Concern.

physical activity was not aimed at finding food, but rather at obtaining further weight loss. Frank et al. (2018) hypothesized that, in subjects with EDs, the psychopathological processes that oppose feeding, including the drive for thinness and body dissatisfaction, could override the normal homeostatic signals on the basis of a fear-driven mechanism. Additionally, food intake loses its positive connotation, being associated with feelings of guilt and shame (Frank, 1991), while dietary restriction and compensatory exercise are gratifying, due to their association with a sense of purity and self-control (Davis and Woodside, 2002; Fassino et al., 2006). Moreover, compensatory exercise has been shown to play a role in emotional regulation in patients with AN (Davis and Woodside, 2002), thus acquiring a reward component linked to the relief of negative emotions. These observations could explain the aberrant food-related reward associated with ED specific psychopathology previously observed by Cowdrey and coll. in a population of AN patients (Cowdrey et al., 2013). In fact, it could be hypothesized that, in underweight patients with EDs, low leptin levels could encourage dietary restraint and compensatory physical exercise instead of determining food seeking. This could be due to the presence of an aberrant food-related reward, which makes losing weight instead of feeding the desirable goal.

As far as self-induced vomiting is concerned, we did not observe a significant association with plasma leptin levels. Even the indirect effect that attempted to illustrate the role of BMI in maintaining this behavior through leptin modifications was not statistically significant. Consequently, these results do not support the hypothesis that self-induced vomiting is favored by a variation of BMI through the modification of blood leptin levels.

4.2. Increased leptin levels and psychopathology

The frequency of binge-eating episodes was found to be positively associated with leptin levels, as previously demonstrated in patients with BED (Adami et al., 2002; Miller et al., 2014; Monteleone et al., 2000b). Leptin levels also resulted positively associated with emotional eating. Indeed, leptin was found to mediate the relationship between BMI and both objective binge eating and emotional eating. As for the "starvation" model, the role of leptin was confirmed only in the presence of high levels of ED specific psychopathology (moderated indirect effect). The present data suggest that in subjects with EDs characterized by an elevated BMI, being overweight plays a role in maintaining objective binge eating and emotional eating through an increase in plasma leptin levels. Again, the proposed model seems to be paradoxically in contrast with the homeostatic functions of leptin itself (Brennan and Mantzoros, 2006). A possible explanation might be a leptin-resistance mechanism triggered by the BMI-dependent increase of leptin levels, considering the well-known association between overweight and a lower sensibility to the anorectic effects of leptin (Enriori et al., 2006). However, since the leptin-resistance mechanism does not fully explain why the model is significant only in the presence of higher levels of ED psychopathology, other factors might be involved. In particular, it could be hypothesized that the relationship between leptin levels and reward-circuits might play a pivotal role. Previous studies have shown that augmented leptin levels determine a chronic inhibition of the dopamine system (Farooqi et al., 2007), which results in an hyper reactivity of the dopaminergic circuits towards external reward-predictive stimuli (Grosshans et al., 2012; Heinz et al., 2004). For this reason, leptin seems to be involved in the maintenance of addictions and in particular in the phenomenon of craving towards the substance of abuse (Aguiar-Nemer et al., 2013; von der Goltz et al., 2010). In a murine model of obesity it has been demonstrated that the excessive ingestion of palatable food determines an overstimulation of dopaminergic systems, in turn inducing a state of reward hyposensitivity and the development of compulsive-like eating (Johnson and Kenny, 2010). The aberrant overeating-related behaviors considered in this study, namely objective binge eating and emotional eating, are associated with reward not only because of the palatability of the ingested food, but they also represent strategies used by ED patients to obtain a relief against negative emotions (Dingemans et al., 2017; Evers et al., 2010). Thus, it can be hypothesized that in ED patients the BMI-dependent leptin-induced inhibition of dopaminergic systems facilitates both objective binge eating and emotional eating through a craving-like mechanism.

The reversed models, based on the hypothesis that leptin alterations are simple consequences of the BMI variation induced by pathological eating behaviors, were not statistically significant, with the exception of compensatory exercise. This result suggests the existence of a two-way effect between leptin levels and compensatory exercise. If on the one hand physical activity contributes to the decrease in body weight and therefore to a lowering of the plasma levels of leptin, the latter could contribute to the maintenance of pathological behavior on a reward-dependent basis. Moreover, it is important to emphasize that, since the moderated models tested in the present study were based on strong a priori hypotheses, the presence or absence of statistical significance of the reverse models does not weaken or strengthen the validity of the original one (Thoemmes, 2015). Furthermore, VIFs related to each of the models were all below the threshold commonly used in collinearity diagnostics (VIF $>$ 10), which allowed to exclude the presence of significant multicollinearity between the variables (Hair et al., 2014). For both the dietary restraint model and the objective binge-eating model it is important to note that a statistically significant indirect effect was identified even in the absence of a total effect, as evidenced by the non-significant multiple linear regressions between BMI and the two variables in question. This apparently controversial phenomenon is actually frequently encountered, can have different causes and does not affect the validity of the indirect effects (Hayes, 2009).

5. Conclusions and limitations

Although the interpretation of these results is limited by the cross-sectional nature of the research design, these findings are consistent with a strong initial hypothesis. They therefore provide a preliminary rationale for further studies on an etiological link between leptin levels variations induced by BMI modifications and the maintenance of reward-related pathological ED behaviors. Indeed, the present study showed that, in ED patients, a low BMI could contribute to the maintenance of dietary restriction and compensatory physical exercise, through a reduction of leptin levels. Vice versa, a high BMI, through an increase of leptin levels, could help to maintain behaviors related to overeating, such as objective binge eating and emotional eating.

The results of the present study should be considered as preliminary, considering the limited sample size and in the light of some limitations, such as the cross-sectional design of the study, which did not allow establishing cause-consequence interactions between variables . In addition, only self-administered questionnaires were used. Finally, body composition measures were not collected, limiting the conclusions regarding the nutritional status of the patients.

If the hypotheses and results of this study were confirmed by longitudinal data on larger samples, the assessment of leptin plasma levels could be integrated into clinical practice to improve the characterization of EDs and to monitor their progress over time. Furthermore, the idea of using leptin-based treatments on subjects affected by specific EDs would be strengthened, as some experts have already suggested for some time (Hebebrand and Özgür., 2012).

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Declaration of Competing Interest

None.

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References

Adami, G., Campostano, A., Cella, F., Scopinaro, N., 2002. Serum leptin concentration in obese patients with binge eating disorder. Int. J. Obes. 26, 1125–1128. https://doi.org/10.1038/sj.ijo.0802010.

Aguiar-Nemer, A.S., Toffolo, M.C.F., da Silva, C.J., Laranjeira, R., Silva-Fonseca, V.A., 2013. Leptin influence in craving and relapse of alcoholics and smokers. J. Clin. Med. Res. 5, 164–167. https://doi.org/10.4021/jocmr1159w.

American Psychiatric Association, 2013. Diagnostic and Statistical Manual of Mental Disorders, fifth ed. American Psychiatric Association, Arlington, VA Arlington, VA. https://doi.org/10.1176/appi.books.9780890425596.744053.

Arnow, B., Kenardy, J., Agras, W.S., 1995. The Emotional Eating Scale: the development of a measure to assess coping with negative affect by eating. Int. J. Eat. Disord. 18, 79–90.

Brennan, A.M., Mantzoros, C.S., 2006. Drug Insight: the role of leptin in human physiology and pathophysiology—emerging clinical applications. Nat. Clin. Pract. Endocrinol. Metab. 2, 318–327. https://doi.org/10.1038/ncpendmet0196.

Brewerton, T.D., Lesem, M.D., Kennedy, A., Garvey, W.T., 2000. Reduced plasma leptin concentrations in bulimia nervosa. Psychoneuroendocrinology 25, 649–658. https://doi.org/10.1016/S0306-4530(00)00016-0.

Buyse, M., Bado, A., Daugé, V., 2001. Leptin decreases feeding and exploratory behaviour via interactions with CCK1 receptors in the rat. Neuropharmacology 40, 818–825. https://doi.org/10.1016/S0028-3908(01)00010-7.

Castellini, G., Lelli, L., Cassioli, E., Ciampi, E., Zamponi, F., Campone, B., Monteleone, A.M., Ricca, V., 2018. Different outcomes, psychopathological features, and co-morbidities in patients with eating disorders reporting childhood abuse: a 3-year follow-up study. Eur. Eat. Disord. Rev. 26. https://doi.org/10.1002/erv.2586.

Castellini, G., Lo Sauro, C., Mannucci, E., Ravaldi, C., Rotella, C.M., Faravelli, C., Ricca, V., 2011. Diagnostic crossover and outcome predictors in eating disorders according to DSM-IV and DSM-V proposed criteria: a 6-year follow-up study. Psychosom. Med. 73, 270–279. https://doi.org/10.1097/PSY.0b013e31820a1838.

Cowdrey, F.A., Finlayson, G., Park, R.J., 2013. Liking compared with wanting for high- and low-calorie foods in anorexia nervosa: aberrant food reward even after weight restoration. Am. J. Clin. Nutr. 97, 463–470. https://doi.org/10.3945/ajcn.112.046011.

Davis, C., Woodside, D.B.B., 2002. Sensitivity to the rewarding effects of food and exercise in the eating disorders. Compr. Psychiatry 43, 189–194. https://doi.org/10.1053/comp.2002.32356.

de Rijke, C.E., Hillebrand, J.J.G., Verhagen, L.A.W., Roeling, T.A.P., Adan, R.A.H., 2005. Hypothalamic neuropeptide expression following chronic food restriction in sedentary and wheel-running rats. J. Mol. Endocrinol. 35, 381–390. https://doi.org/10.1677/jme.1.01808.

Derogatis, L.R., Lipman, R.S., Covi, L., 1973. SCL-90: an outpatient psychiatric rating scale–preliminary report. Psychopharmacol. Bull. 9, 13–28.

Dingemans, A., Danner, U., Parks, M., 2017. Emotion regulation in binge eating disorder: a review. Nutrients 9, 1274. https://doi.org/10.3390/nu9111274.

Enriori, P.J., Evans, A.E., Sinnayah, P., Cowley, M.A., 2006. Leptin resistance and obesity. Obesity 14, 254S–258S. https://doi.org/10.1038/oby.2006.319.

Evers, C., Stok, F., de Ridder, D.T.D., 2010. Feeding your feelings: emotion regulation strategies and emotional eating. Personal. Soc. Psychol. Bull. 36, 792–804. https://doi.org/10.1177/0146167210371383.

Exner, C., Hebebrand, J., Remschmidt, H., Wewetzer, C., Ziegler, A., Herpertz, S., Schweiger, U., Blum, W.F., Preibisch, G., Heldmaier, G., Klingenspor, M., 2000. Leptin suppresses semi-starvation induced hyperactivity in rats: implications for anorexia nervosa. Mol. Psychiatry 5, 476–481. https://doi.org/10.1038/sj.mp.4000771.

Fairburn, C.G., 2008. Cognitive Behavior Therapy and Eating Disorders. Guilford Press.

Farooqi, I.S., Bullmore, E., Keogh, J., Gillard, J., O'Rahilly, S., Fletcher, P.C., 2007. Leptin regulates striatal regions and human eating behavior. Science 317, 1355. 1355. https://doi.org/10.1126/science.1144599.

Fassino, S., Pierò, A., Gramaglia, C., Daga, G.A., Gandione, M., Rovera, G.G., Bartocci, G., 2006. Clinical, psychological, and personality correlates of asceticism in anorexia nervosa: from saint anorexia to pathologic perfectionism. Transcult. Psychiatry 43, 600–614. https://doi.org/10.1177/1363461506070785.

Ferron, F., Considine, R.V., Peino, R., Lado, I.G., Dieguez, C., Casanueva, F.F., 1997. Serum leptin concentrations in patients with anorexia nervosa, bulimia nervosa and non-specific eating disorders correlate with the body mass index but are independent of the respective disease. Clin. Endocrinol. (Oxf). 46, 289–293. https://doi.org/10.1046/j.1365-2265.1997.1260938.x.

Frank, E.S., 1991. Shame and guilt in eating disorders. Am. J. Orthopsychiatry 61, 303–306. https://doi.org/10.1037/h0079241.

Frank, G.K.W., Deguzman, M.C., Shott, M.E., Laudenslager, M.L., Rossi, B., Pryor, T., 2018. Association of brain reward learning response with harm avoidance, weight gain, and hypothalamic effective connectivity in adolescent anorexia nervosa. JAMA Psychiatry 75, 1071–1080. https://doi.org/10.1001/jamapsychiatry.2018.2151.

Grosshans, M., Vollmert, C., Dt-Klein, S.V., Tost, H., Leber, S., Bach, P., Hler, M.B., Von Der Goltz, C., Mutschler, J., Loeber, S., Hermann, D., Wiedemann, K., Meyer-Lindenberg, A., Kiefer, F., 2012. Association of leptin with food cue-induced activation in human reward pathways. Arch. Gen. Psychiatry 69, 529–537. https://doi.org/10.1001/archgenpsychiatry.2011.1586.

Hayes, A.F., 2013. Introduction to mediation, moderation, and conditional process analysis: a regression-based approach. Guilford Publications. The Guilford Press.

Hair, J.F., Black, W.C., Babin, B.J., Anderson, R.E., 2014. Multivariate data analysis. Multivariate data analysis, seventh ed. Pearson, Harlow.

Hayes, A.F., 2009. Beyond Baron and Kenny: statistical mediation analysis in the new millennium. Commun. Monogr. 76, 408–420. https://doi.org/10.1080/03637750903310360.

Hebebrand, J., Blum, W.F., Barth, N., Coners, H., Englaro, P., Juul, A., Ziegler, A., Warnke, A., Rascher, W., Remschmidt, H., 1997. Leptin levels in patients with anorexia nervosa are reduced in the acute stage and elevated upon short-term weight restoration. Mol. Psychiatry 2, 330–334. https://doi.org/10.1038/sj.mp.4000282.

Hebebrand, J., Özgür, A., 2012. Leptin treatment of patients with anorexia nervosa? The urgent need for initiation of clinical studies. Eur. Child Adolesc. Psychiatry. https://doi.org/10.1007/s00787-012-0243-3.

Heinz, A., Siessmeier, T., Wrase, J., Hermann, D., Klein, S., Grüsser, S.M., Grüsser-Sinopoli, S.M., Flor, H., Braus, D.F., Buchholz, H.G., Gründer, G., Schreckenberger, M., Smolka, M.N., Rösch, F., Mann, K., Bartenstein, P., 2004. Correlation between dopamine D(2) receptors in the ventral striatum and central processing of alcohol cues and craving. Am. J. Psychiatry 161, 1783–1789. https://doi.org/10.1176/appi.ajp.161.10.1783.

Holtkamp, K., Herpertz-Dahlmann, B., Hebebrand, K., Mika, C., Kratzsch, J., Hebebrand, J., 2006. Physical activity and restlessness correlate with leptin levels in patients with adolescent anorexia nervosa. Biol. Psychiatry 60, 311–313. https://doi.org/10.1016/j.biopsych.2005.11.001.

IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.

Jimerson, D.C., Mantzoros, C., Wolfe, B.E., Metzger, E.D., 2000. Decreased serum leptin in bulimia nervosa. J. Clin. Endocrinol. Metab. 85, 4511–4514. https://doi.org/10.1210/jcem.85.12.7051.

Johnson, P.M., Kenny, P.J., 2010. Dopamine D2 receptors in addiction-like reward dysfunction and compulsive eating in obese rats. Nat. Neurosci. 13, 635–641. https://doi.org/10.1038/nn.2519.

Karageorgiou, V., Furukawa, T.A., Tsigkaropoulou, E., Karavia, A., Gournellis, R., Soureti, A., Bellos, I., Douzenis, A., Michopoulos, I., 2019. Adipokines in anorexia nervosa: a systematic review and meta-analysis. Psychoneuroendocrinology. https://doi.org/10.1016/j.psyneuen.2019.104485.

Leinninger, G.M., Jo, Y.-H., Leshan, R.L., Louis, G.W., Yang, H., Barrera, J.G., Wilson, H., Opland, D.M., Faouzi, M.A., Gong, Y., Jones, J.C., Rhodes, C.J., Chua, S., Diano, S., Horvath, T.L., Seeley, R.J., Becker, J.B., Münzberg, H., Myers, M.G., 2009. Leptin acts via leptin receptor-expressing lateral hypothalamic neurons to modulate the mesolimbic dopamine system and suppress feeding. Cell Metab. 10, 89–98. https://doi.org/10.1016/j.cmet.2009.06.011.

Leslie, M., Turton, R., Burgess, E., Nazar, B.P., Treasure, J., 2018. Testing the addictive appetite model of binge eating: the importance of craving, coping, and reward

enhancement. Eur. Eat. Disord. Rev. 26, 541–550. https://doi.org/10.1002/erv.2621.

Meye, F.J., Adan, R.A.H., 2014. Feelings about food: the ventral tegmental area in food reward and emotional eating. Trends Pharmacol. Sci. 35, 31–40. https://doi.org/10.1016/J.TIPS.2013.11.003.

Michels, N., Sioen, I., Ruige, J., De Henauw, S., 2017. Children's psychosocial stress and emotional eating: a role for leptin? Int. J. Eat. Disord 50, 471–480. https://doi.org/10.1002/eat.22593.

Miller, R., Tanofsky-Kraff, M., Shomaker, L.B., Field, S.E., Hannallah, L., Reina, S.A., Mooreville, M., Sedaka, N., Brady, S.M., Condarco, T., Reynolds, J.C., Yanovski, S.Z., Yanovski, J.A., 2014. Serum leptin and loss of control eating in children and adolescents. Int. J. Obes. (Lond). 38, 397–403. https://doi.org/10.1038/ijo.2013.126.

Monteleone, A.M., Castellini, G., Volpe, U., Ricca, V., Lelli, L., Monteleone, P., Maj, M., 2018. Neuroendocrinology and brain imaging of reward in eating disorders: a possible key to the treatment of anorexia nervosa and bulimia nervosa. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 80, 132–142. https://doi.org/10.1016/j.pnpbp.2017.02.020.

Monteleone, P., 2002. Leptin secretion is related to chronicity and severity of the illness in bulimia nervosa. Psychosom. Med. 64, 874–879. https://doi.org/10.1097/01.PSY.0000024239.11538.A5.

Monteleone, P., Bortolotti, F., Fabrazzo, M., La Rocca, A., Fuschino, A., Maj, M., 2000a. Plasma leptin response to acute fasting and refeeding in untreated women with bulimia nervosa. J. Clin. Endocrinol. Metab. 85, 2499–2503. https://doi.org/10.1210/jcem.85.7.6673.

Monteleone, P., Di Lieto, A., Tortorella, A., Longobardi, N., Maj, M., 2000b. Circulating leptin in patients with anorexia nervosa, bulimia nervosa or binge-eating disorder: relationship to body weight, eating patterns, psychopathology and endocrine changes. Psychiatry Res. 94, 121–129. https://doi.org/10.1016/S0165-1781(00)00144-X.

Monteleone, P., Fabrazzo, M., Tortorella, A., Fuschino, A., Maj, M., 2002. Opposite modifications in circulating leptin and soluble leptin receptor across the eating disorder spectrum. Mol. Psychiatry 7, 641–646. https://doi.org/10.1038/sj.mp.4001043.

Monteleone, P., Maj, M., 2013. Dysfunctions of leptin, ghrelin, BDNF and endocannabinoids in eating disorders: beyond the homeostatic control of food intake. Psychoneuroendocrinology 38, 312–330. https://doi.org/10.1016/J.PSYNEUEN.2012.10.021.

Monti, V., Carlson, J.J., Hunt, S.C., Adams, T.D., 2006. Relationship of ghrelin and leptin hormones with body mass index and waist circumference in a random sample of adults. J. Am. Diet. Assoc. 106, 822–828. https://doi.org/10.1016/j.jada.2006.03.015.

Pearson, C.M., Wonderlich, S.A., Smith, G.T., 2015. A risk and maintenance model for bulimia nervosa: from impulsive action to compulsive behavior. Psychol. Rev. 122, 516–535. https://doi.org/10.1037/a0039268.

Penaforte, F.R., de, O., Minelli, M.C.S., Rezende, L.A., Japur, C.C., 2019. Anxiety symptoms and emotional eating are independently associated with sweet craving in young adults. Psychiatry Res. 271, 715–720. https://doi.org/10.1016/j.psychres.2018.11.070.

Striegel-Moore, R.H., Cachelin, F.M., 2001. Etiology of eating disorders in women. Couns. Psychol. 29, 635–661. https://doi.org/10.1177/0011000001295002.

Thoemmes, F., 2015. Reversing arrows in mediation models does not distinguish plausible models. Basic Appl. Soc. Psych. 37, 226–234. https://doi.org/10.1080/01973533.2015.1049351.

Verhagen, L.A.W., Luijendijk, M.C.M., Adan, R.A.H., 2011. Leptin reduces hyperactivity in an animal model for anorexia nervosa via the ventral tegmental area. Eur. Neuropsychopharmacol. 21, 274–281. https://doi.org/10.1016/j.euroneuro.2010.11.006.

Volkow, N.D., Wang, G.-J., Fowler, J.S., Tomasi, D., Telang, F., 2011. Addiction: beyond dopamine reward circuitry. Proc. Natl. Acad. Sci. 108, 15037–15042. https://doi.org/10.1073/pnas.1010654108.

von der Goltz, C., Koopmann, A., Dinter, C., Richter, A., Rockenbach, C., Grosshans, M., Nakovics, H., Wiedemann, K., Mann, K., Winterer, G., Kiefer, F., 2010. Orexin and leptin are associated with nicotine craving: a link between smoking, appetite and reward. Psychoneuroendocrinology 35, 570–577. https://doi.org/10.1016/j.psyneuen.2009.09.005.

von Prittwitz, S., Blum, W.F., Ziegler, A., Scharmann, S., Remschmidt, H., Hebebrand, J., 1997. Restrained eating is associated with low leptin levels in underweight females. Mol. Psychiatry 2, 420–422.