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The association of leptin secretion with cognitive performance in patients with eating disorders

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ABSTRACT

This study is an investigation of neuropsychological performance in patients with anorexia nervosa, bulimia nervosa, and binge eating disorder and hormonal secretion patterns for ghrelin, leptin, insulin, and glucose. An oral glucose tolerance test (OGTT) was performed in a cohort of $n = 30$ female patients suffering from eating disorders as well as $n = 20$ control females. All participants underwent the Wisconsin Card Sorting Test (WCST), the Trail Making Test (TMT), and a go/no-go task using food vs. neutral stimuli. Patients with anorexia nervosa differed from controls in their leptin response to the OGTT. While the four groups under investigation did not differ in neuropsychological performance, we found leptin responses to the OGTT to be associated with performance in the food-specific go/no-go task. These preliminary results may indicate a putative association between leptin concentrations and neuropsychological performance, particularly in measures of inhibitory control. Further studies investigating the role of leptin in impulsive behaviors in eating disorders would be useful.

1. Introduction

Anorexia nervosa (AN) is characterized by restrictive eating patterns, being underweight, and the fear of gaining weight. Patients with AN are capable of suppressing food intake, even in the presence of strong physiological signals of hunger. Bulimia nervosa (BN) is characterized by regular episodes of binge eating with loss of control followed by compensatory behaviors such as vomiting or laxative use in an effort to control weight. Binge eating and loss of control also occur in binge eating disorder (BED) but are not followed by compensatory behaviors; obesity or overweight are common (APA, 2013). High vs. low behavioral inhibitory control defines the clinical phenotypes of AN vs. BN and BED.

Inhibitory control is the ability to suppress or interrupt a response (Bari and Robbins, 2013). Although various experimental paradigms can be used to assess inhibitory control, go/no-go tasks are often used in eating disorder (ED) research to assess the ability to inhibit a response that has not been initiated. Commission errors (i.e., failures to inhibit "no-go trials") and reaction times for "go-trials" are measures of performance in go/no-go tasks. Systematic reviews of research in this area have indicated that, in comparison to controls, BN and BED are associated with inhibitory control deficits in go/no-go tasks (Wu et al., 2013; Lavagnino et al., 2016). In addition, greater inhibitory control deficits have been noted for disorder-relevant stimuli (e.g., food) in BN (Wu et al., 2013) and BED (Kittel et al., 2015; Giel et al., 2017). However, inhibitory control deficits are also associated with obesity (Lavagnino et al., 2016; Giel et al., 2017) and findings regarding inhibitory control in BED are mixed and ambiguous (e.g., Svaldi et al., 2015; Manasse et al., 2016; Kittel et al., 2017). Studies applying food stimuli have not been conducted with AN participants, but emotional stimuli have been shown to inhibit responses in a go/no-go task (Hildebrandt et al., 2016).

Representing the opposite side of inhibitory control, increased cognitive control and inflexibility may be responsible for the rigid eating behaviors seen in AN. In neuropsychological investigations, set-shifting paradigms are used to assess cognitive flexibility. Set-shifting is

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the ability to shift thoughts and actions in response to changing contexts. In EDs, set-shifting has frequently been assessed with perseverative errors in the Wisconsin Card Sorting Test (WCST; Heaton et al., 1993) and task completion time in the Trail Making Test (TMT; Reitan, 1992). Impaired set-shifting abilities have been documented for patients with AN (e.g., Holliday et al., 2005; Lang et al., 2014; Westwood et al., 2016; Smith et al., 2018). However, differing methodologies have yielded discrepant results (Lang et al., 2014). In the systematic review by van den Eynde et al. (2011), two studies showed impaired set-shifting, using the WCST, in BN and BED compared to controls; two other studies found no differences. In the most comprehensive meta-analysis conducted, Wu et al. (2014) claim that poor set-shifting is present across all EDs compared to controls (Wu et al., 2014). Mixed results were yielded in the review by Kittel et al. (2015). Set-shifting deficits were found in BED, as compared to obese individuals using the TMT, and in obese patients with BED, as compared to obese individuals using the WCST; furthermore, there were no differences in the WCST between patients with BED and normal-weight controls (Kittel et al., 2015). Patients with BN performed worse than controls in both the TMT and WCST in the meta-analysis conducted by Hirst et al. (2017), although no evidence of set-shifting impairments was found in certain singular studies (e.g., Zakzanis et al., 2010). In the most recent systematic review on set-shifting across EDs, including 12 previous systematic reviews (six of which were meta-analytic reviews), Smith et al. (2018) concluded there is little evidence for set-shifting differences between ED diagnostic groups. Specific set-shifting tasks may be responsible for the varied results mentioned above (Wu et al., 2014; Smith et al., 2018). Moreover, age may be a significant factor. Westwood et al. (2016) focused on the WCST and found effect sizes for deficits in set-shifting in AN were greater in adults, as compared to children and adolescents.

It remains unclear whether neuropsychological impairments across EDs function as etiopathogenetic or maintenance factors (Smith et al., 2018). Impaired neuropsychological performance has been linked to hormonal alterations regarding the hypothalamus-pituitary-adrenal axis and the hypothalamus-pituitary-gonadal axis, mostly in AN (e.g., Sherwin, 2007; Chui et al., 2008; Buehren et al., 2011). Similar studies in BN and BED have not been conducted. Studies examining the association between appetite-regulating hormones and neuropsychological performance in EDs are also lacking.

This pilot study aims to contribute to this knowledge gap by assessing both neuropsychological performance and appetite-regulating hormones in participants with AN, BN, and BED, as well as controls. Appetite-regulating hormones are commonly assessed under standardized (e.g., fasting) conditions, in a single and static baseline procedure. In contrast, this study examines appetite-regulating hormonal systems with a dynamic functional test procedure instead of with a single measure. Since food intake is the physiological stimulus for changes in secretion of the hormones of interest, the paradigm of oral glucose ingestion after an overnight fast employing an oral glucose tolerance test (OGTT) has been applied. In addition to glucose and insulin, the hormones commonly assessed during the OGTT, leptin and ghrelin were also examined as these two appetite-regulating hormones have recently been associated with cognitive performance (e.g., Yin et al., 2018, Chen et al., 2017). The “net” hormonal response during the OGTT was assessed by calculating the area under the curve (AUC), corrected for baseline, since baseline concentrations were expected to significantly differ between groups and thus influence the overall secretion patterns. Additionally, a set-shifting variant of a food vs. neutral stimuli go/no-go task was applied, examining the combined impulsivity control x set-shifting abilities. We included only obese BED patients to assess a phenotype that may be characterized by more distinct impairments in cognitive performance. Not only has poor inhibitory control been associated with high BMI (Stice et al., 2016), but greater impairments in executive function have been found in obese patients with BED, as compared to patients with only BED (e.g., Duchesne et al., 2010; Manasse et al., 2015). Similarly, in the context of food, greater impairments in response inhibition have been observed in obese patients with BED, as compared to obese individuals without BED (e.g., Schag et al., 2013; Svaldi et al., 2014; Hege et al., 2015).

We hypothesized that:

1) Hormone secretion patterns would significantly differ between patients with EDs and controls, and
2) Dysfunctional hormone secretion patterns in patients with AN, BN, and BED would be associated with impaired performance in the applied variant of the go/no-go task. Since there is no previous research associating appetite-regulating peptides with neuropsychological performance in EDs, and findings related to associations between endocrine responses and cognitive performance in different clinical cohorts are inconsistent, no hypotheses related to specific hormones or diagnostic subgroups were formulated.

2. Material and methods

2.1. Study population

Participants were adult female outpatients and inpatients diagnosed with AN ($n = 10$), BN ($n = 10$) and BED ($n = 10$). Participants were recruited during their inpatient stay or outpatient consultation at the Department of Psychosomatic Medicine and Psychotherapy at the University Hospital Erlangen, Germany. Diagnoses of AN, BN, and BED were ascertained during non-standardized, semi-structured clinical interviews conducted by psychologists and physicians with experience in the assessment and treatment of EDs. Inpatients took part in the investigation within three days of admission, to rule out treatment effects on hormone levels and neuropsychological performance. Inclusion criteria were: 1. female; 2. diagnosis of AN, BN, and BED according to the Diagnostic and Statistical Manual of Mental Disorders (APA, 2013); 3. BMI $\leq$ 18.5 kg/m^2 for AN, 18.5 kg/m^2 $<$ BMI $\leq$ 25 kg/m^2 for BN, and BMI $\geq$ 30 kg/m^2 for BED; 4. age $\geq$ 18 years; and 5. able to provide written informed consent. Exclusion criteria were acute psychiatric diagnoses other than major depression; e.g., psychosis or acute substance dependence.

Female controls (CO, $n = 20$) consisted of medical students or medical staff (e.g., nurses, laboratory staff, medical professionals) unfamiliar with the study subject and unfamiliar with the researcher. CO were over 18, had a BMI within norms (18.5 kg/m^2 $<$ BMI $\leq$ 25 kg/m^2), scored in the normal range on the eating disorder-specific questionnaires and reported the absence of ED-related symptoms (e.g., restrictive eating patterns, binge eating episodes or purging) or an ED diagnosis at the time of participation and in the past.

Participant recruitment was conducted in a sequential manner, until the desired number of participants was reached. The study was approved by the local ethics committee; all participants provided written informed consent following a detailed description of the study´s objectives.

2.2. Data collection

Participants were tested at 08:00 am after an overnight fast. Participants were weighed before the test procedure to calculate the BMI. The test procedure started with an OGTT, followed by the administration of self-report measures and neuropsychological tasks. Questionnaires were immediately checked for missing data and participants were asked to complete any missing items.

2.3. Measures

2.3.1. Eating Disorder Examination-Questionnaire (EDE-Q)

The paper-and-pencil version of the EDE-Q (Fairburn and Beglin, 1994) evaluates ED psychopathology over the past 28 days. It

contains 22 items on a seven-point scale ranging from “never” to “every day”. There are four subscales assessing the following: a) restraint, b) eating concern, c) weight concern, and d) shape concern. Internal consistency of the German version was $\alpha = 0.97$ in the validation study (Hilbert et al., 2007).

2.3.2. Eating Disorder Inventory-2 (EDI-2)

The EDI-2 (Paul and Thiel, 2005) is a paper-and-pencil self-report questionnaire with 91 items assessing ED psychopathology, as well as interpersonal and intrapersonal aspects considered relevant for the development and perpetuation of EDs (e.g., perfectionism, interpersonal distrust, and lack of interoceptive awareness). Only the total score was considered in the analyses.

2.3.3. Patient Health Questionnaire for the assessment of depression (PHQ-9)

This brief paper-and-pencil instrument was applied as a measure of depression according to Löwe et al. (2004).

2.4. Blood sampling for assessment of appetite-regulating hormones during an OGTT

An oral glucose tolerance test (OGTT) was performed by the oral ingestion of 75 g glucose after an overnight fast; plasma levels of ghrelin, leptin, insulin, and glucose were determined at 0 (t0), 30 (t1), 60 (t2), 90 (t3), and 120 (t4) minutes following glucose ingestion. Blood samples were kept on ice and transported to the laboratory, where they were immediately centrifuged at 3500 rpm at 4 °C for plasma separation. Plasma was aliquoted and stored at −20 °C. All hormone measures were performed at once after the completion of the study. The quantitative measurement of leptin and total ghrelin in plasma was performed using a leptin Sandwich ELISA kit from Mediagnost, (Reutlingen, Germany) and a sandwich ghrelin ELISA from Merck (Darmstadt, Germany), according to the manufacturer's instructions. Inter-assay and intra-assay reproducibility were analyzed by the manufacturers by determining the coefficient of variation, which was 12% and 5% on average for leptin and 1–2% and 5–8% for ghrelin, respectively. Plasma glucose was measured by the enzymatic hexokinase method (cobas 501, Roche, Mannheim, Germany). Insulin was determined using the Roche cobas E411 analyzer (Roche, Mannheim, Germany) via the electrochemiluminescence assay (ECLIA).

2.5. Neuropsychological performance using a go/no-go paradigm with food vs. neutral stimuli, the WCST, and TMT

A go/no-go shifting task (Meule et al., 2014) was administered to assess impairment of inhibitory control in response to food-related and control stimuli. The task consisted of 16 blocks with 18 trials. In each block, half of the pictures served as targets; the other half served as distractors. At the beginning of each block, the target category was defined; participants were instructed to respond as quickly as possible to target stimuli, but to withhold their response to the distractors. In eight blocks, the target categories were foods, and neutral objects served as distractors; in the remaining eight blocks, the target categories were neutral objects, and foods served as distractors. Blocks were presented in two different orders, with the order of blocks counterbalanced across subjects. If the target category changed from one block to the next, the second block was defined as a “shift block”; in the “non-shift” blocks, the category was the same. The task was programmed with the Presentation® software (Version 16.0, Neurobehavioral Systems, Inc., Albany, CA, USA).

The WCST (Heaton et al., 1993) and the TMT (Reitan, 1992) were applied as standard tests of cognitive function. The WCST asks participants to form abstract concepts, shift and maintain categorization options, and adapt their strategies in response to feedback; it is considered as a test for set-shifting/frontal brain function. The TMT is another test to assess executive function and set-shifting. Total number of correct responses, total number of errors, total number of perseveration errors, and number of attempts to complete a category were assessed for the WCST. The TMT-B to TMT-A ratio (B/A) was calculated as the ratio of task completion time in milliseconds (ms), for TMT-B to TMT-A serving as an indicator of deficits of cognitive flexibility/task-switching (Arbuthnott and Frank, 2000).

2.6. Data analyses

In a coordinate system with the x-axis depicting time (t0, t1, t2, t3, and t4 being the 5 time assessment points during the OGTT) and the y-axis depicting hormone concentrations (C0-C4, respectively), the AUCs, representing the area between the hormone curves and x-axis, were calculated to evaluate hormonal secretion patterns using the trapezoid rule. Thereafter, the AUCs were corrected for diverging baseline hormone concentrations between groups by subtracting the area C0 x t0 ($= AUC_{corr.}$). The correction for baseline level was necessary to assess the “net” hormonal responses. Commission errors (CEs) and reaction times (RTs in ms) were assessed as outcome measures of the go/no-go paradigm. CE and RT in the go/no-go paradigm have been reported as the means.

Statistical analyses were performed using SPSS (IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.). *T*-tests for comparisons within groups, analyses of variance (ANOVA) or multivariate analyses of variance (MANOVA) and post hoc tests for comparisons between groups were performed (e.g., Games-Howell in the case of unequal variances). In the case of the go/no-go paradigm, repeated-measures analyses of variance (rm-ANOVA) were performed. Two repeated measure factors were defined: (a) “category” for food vs. neutral stimuli content and (b) “shift condition” for shift vs. non-shift blocks. To control for the possible confounding effects of group differences regarding depression, the analyses were re-run with the PHQ-9 as a covariate. To examine the statistical predictive value of different independent variables with regard to the number of commission errors in response to food-related stimuli, a stepwise multiple linear regression was performed with RT to food-related stimuli as a control variable and group, as well as AUCcorr. for leptin and the group by AUCcorr. for leptin interaction as the predictor variables.

The level of significance was set at $p \leq 0.05$. However, a Bonferroni correction for multiple tests was performed according to the number of independent variables in each hypothesis.

3. Results

3.1. Age, BMI, eating disorder-specific psychopathology

There were no significant differences between the groups regarding age ($F_{3,46} = 2.65$, $p = 0.06$, partial $\eta^2 = 0.15$). As expected, the ANOVA revealed a significant main effect for group regarding BMI ($F_{3,46} = 50.20$, $p < 0.001$, partial $\eta^2 = 0.77$), with AN < BN ($p = 0.003$), AN < CO ($p < 0.001$), AN < BED ($p < 0.001$), BN < BED ($p = 0.001$), and CO < BED ($p = 0.001$) in corresponding post hoc tests (Games-Howell) (Table 1).

The groups also differed on the EDE-Q ($F_{3,46} = 41.43$, $p < 0.001$, partial $\eta^2 = 0.73$); post hoc tests (Games-Howell) revealed differences only between EDs and CO (AN vs. CO: $p = 0.009$, BN vs. CO: $p < 0.001$, BED vs. CO: $p < 0.001$), but not between the diagnostic subgroups of ED. The same pattern was observed for the total scores on the EDI-2 ($F_{3,46} = 26.68$, $p < 0.001$, partial $\eta^2 = 0.64$; AN vs. CO: $p = 0.03$, BN vs. CO: $p < 0.001$, BED vs. CO: $p < 0.001$ using Games-Howell) (Table 1).

There was also a main effect for group on the PHQ-9 ($F_{3,46} = 16.68$, $p < 0.001$, partial $\eta^2 = 0.52$). ED patients had higher scores than CO, as shown via Games-Howell post hoc testing (AN vs. CO: $p = 0.01$, BN vs. CO: $p = 0.001$, BED vs. CO: $p = 0.001$) (Table 1).

Table 1
The table displays mean values ± standard deviations with regard to age (in years), body mass index (BMI, in kg/m^2), and the self-report questionnaires Eating Disorder Examination-Questionnaire (EDE-Q), Eating Disorder Inventory-2 (EDI-2) and Patient Health Questionnaire-9 (PHQ-9) for each group.

	AN $n = 10$	BN $n = 10$	BED $n = 10$	CO $n = 20$	ANOVA
Age	29.50 ± 11.58	29.00 ± 11.02	40.60 ± 8.07	34.85 ± 11.06	$F_{3,46} = 2.65$, $p = 0.06$
BMI	16.37 ± 1.43	23.77 ± 4.68	42.70 ± 10.28	21.80 ± 2.09	$F_{3,46} = 50.20$, $\mathbf{p < 0.001}$
EDE-Q	2.76 ± 1.75	4.12 ± 0.75	3.54 ± 1.06	0.41 ± 0.35	$F_{3,46} = 41.43$, $\mathbf{p < 0.001}$
EDI-2	281.80 ± 93.00	353.10 ± 51.21	329.50 ± 56.91	181.65 ± 31.97	$F_{3,46} = 26.68$, $\mathbf{p < 0.001}$
PHQ-9	11.80 ± 6.88	14.10 ± 6.31	13.40 ± 6.02	2.80 ± 2.12	$F_{3,46} = 16.68$, $\mathbf{p < 0.001}$

3.2. Hormonal regulation

Multivariate ANOVA (MANOVA) with AUCcorr. for ghrelin, leptin, insulin, and glucose as the dependent variables, and group (AN vs. BN vs. BED vs. CO) as the between-subject factor, showed a statistically significant difference between groups based on "net" hormonal responses regarding the hormones under investigation ($F_{12,114.06} = 2.59$, $p = 0.004$, Wilk's $\Lambda = 0.53$, partial $\eta^2 = 0.19$).

The between-subjects effects were significant for leptin ($F_{3,46} = 5.40$, $p = 0.003$, partial $\eta^2 = 0.26$) and glucose ($F_{3,46} = 3.45$, $p = 0.02$, partial $\eta^2 = 0.18$), but not for ghrelin ($F_{3,46} = 2.20$, $p = 0.10$, partial $\eta^2 = 0.13$), or insulin ($F_{3,46} = 2.32$, $p = 0.09$, partial $\eta^2 = 0.13$). Following Bonferroni correction with the new level of significance set at 0.01, only the significant result for leptin remained.

Post hoc tests for leptin (Games-Howell) showed a significantly different net hormonal response when comparing AN and CO ($p = 0.02$) (Fig. 1a–d).

$AUC_{corr.}$ for leptin and scores in the ED-specific questionnaires were not correlated ($p \geq 0.19$, data not shown).

3.3. Go/no-go test

3.3.1. Commission errors CE

The repeated measures ANOVA (rm-ANOVA) with 2 repeated measures factors ("category": food vs. neutral stimuli and "shift condition": shift vs. non-shift) and group (AN vs. BN vs. BED vs. CO) as the between-subject factor revealed a main effect for category ($F_{1,46} = 14.24$, $p < 0.001$, partial $\eta^2 = 0.24$), with more commission errors in response to food stimuli, and for shift condition ($F_{1,46} = 20.71$, $p < 0.001$, partial $\eta^2 = 0.31$), with more commission errors for shift (i.e., when target category was changed). However, there was no main effect for group ($F_{3,46} = 1.49$, $p = 0.23$, partial $\eta^2 = 0.09$).

These results are shown in Fig. 2a–b.

Mean values ± standard deviations (SD) for commission errors (CE) are shown in Table 2.

3.3.2. Reaction times RT

The rm-ANOVA with 2 repeated measures factors ("category": food vs. neutral stimuli and "shift condition": shift vs. non-shift) and group (AN vs. BN vs. BED vs. CO) as the between-subject factor revealed no main effect for group ($F_{3,46} = 1.25$, $p = 0.30$, partial $\eta^2 = 0.08$), but a main effect for category ($F_{1,46} = 17.21$, $p < 0.001$, partial $\eta^2 = 0.27$), indicating that, averaged across other factors, RT for food stimuli were significantly faster than for neutral objects.

These results are displayed in Fig. 3.

Mean values ± standard deviations (SD) for reaction times (RT) are shown in Table 2.

3.4. Wisconsin Card Sorting Test, Trail Making Test-A and -B

The multivariate analysis of variance (MANOVA) using the total number of errors, the total number of perseverations, the total number of perseverative errors, and the total number of cards to complete the first category as dependent variables of the WCST showed a main effect for group ($F_{12,114.06} = 2.16$, $p = 0.02$, Wilks $\Lambda = 0.58$, partial $\eta^2 = 0.17$) (Table 3). Subsequent ANOVAs revealed main effects for group regarding the total number of errors ($F_{3,46} = 3.30$; $p = 0.03$, partial $\eta^2 = 0.18$) and the total number of cards to complete the first category ($F_{3,46} = 3.00$; $p = 0.04$, partial $\eta^2 = 0.16$). However, these results were no longer significant with Bonferroni correction for multiple comparisons and p set at 0.01.

ANOVA with TMA B/A ratio as the dependent variable showed no main effect for group ($F_{3,46} = 1.21$; $p = 0.32$, partial $\eta^2 = 0.07$) (Table 3).

To control for possible confounding effects of group differences with regard to depression, all analyses (3.3 and 3.4) were re-run with the PHQ-9 as a covariate. However, this did not affect group differences.

3.5. Hormonal prediction of neuropsychological performance in the go/no-go paradigm

A stepwise multiple linear regression analysis predicting CE in response to food stimuli, yielded a significant model ($F_{2,47} = 8.92$, $p = 0.001$, $R^2 = 0.28$). AUCcorr. for leptin ($\beta = 0.32$, $p = 0.01$) and RT in response to food stimuli ($\beta = 0.40$, $p = 0.003$) were significant predictors. All other variables were not significant ($p \geq 0.41$). Results are displayed in Table 4. Creating predicted values from the regression equation, a scatter plot to depict the multiple regression model R2 value is shown in Fig. 4.

A similar procedure for statistical prediction of CE in response to neutral stimuli did not lead to a significant model; similar findings were observed with regard to set-shifting performance.

Correlations between hormonal responses and scores in ED-related questionnaires are included in the supplementary Table S1.

4. Discussion

This study examined female patients with AN, BN, and BED, and female controls, to find that patients with AN differ from controls regarding their "net" (i.e., corrected for baseline concentrations) leptin response during an OGTT. While the four groups being compared did not differ in their neuropsychological performance in a set-shifting go/no-go paradigm with food vs. neutral stimuli, leptin responses in the OGTT were found to be associated with performance in response inhibition toward food-associated stimuli (the number of commission errors in response to food) in the go/no-go task. Disturbed concentrations in appetite-regulating circuits in EDs have been reviewed elsewhere (e.g., Baskaran et al., 2017; Schorr and Miller, 2017). Changes in appetite-regulating hormones have been suggested to represent homeostatic adaptations to an altered energy balance and to determine the acquisition and/or maintenance of undernutrition or binge eating, both of which may be rewarding for patients (Monteleone et al., 2018). The assessment of baseline peripheral hormonal levels, however, may not show differences between the diagnostic groups; e.g., peripheral levels of leptin in patients with bulimia nervosa -even in the acute phase- have been found to be either lower or not to differ from those in healthy controls (Smitka et al., 2013). Similarly, peripheral ghrelin levels in the acute phase of bulimia nervosa have been found to be higher than in controls or to not differ (Smitka et al., 2013). Such observations

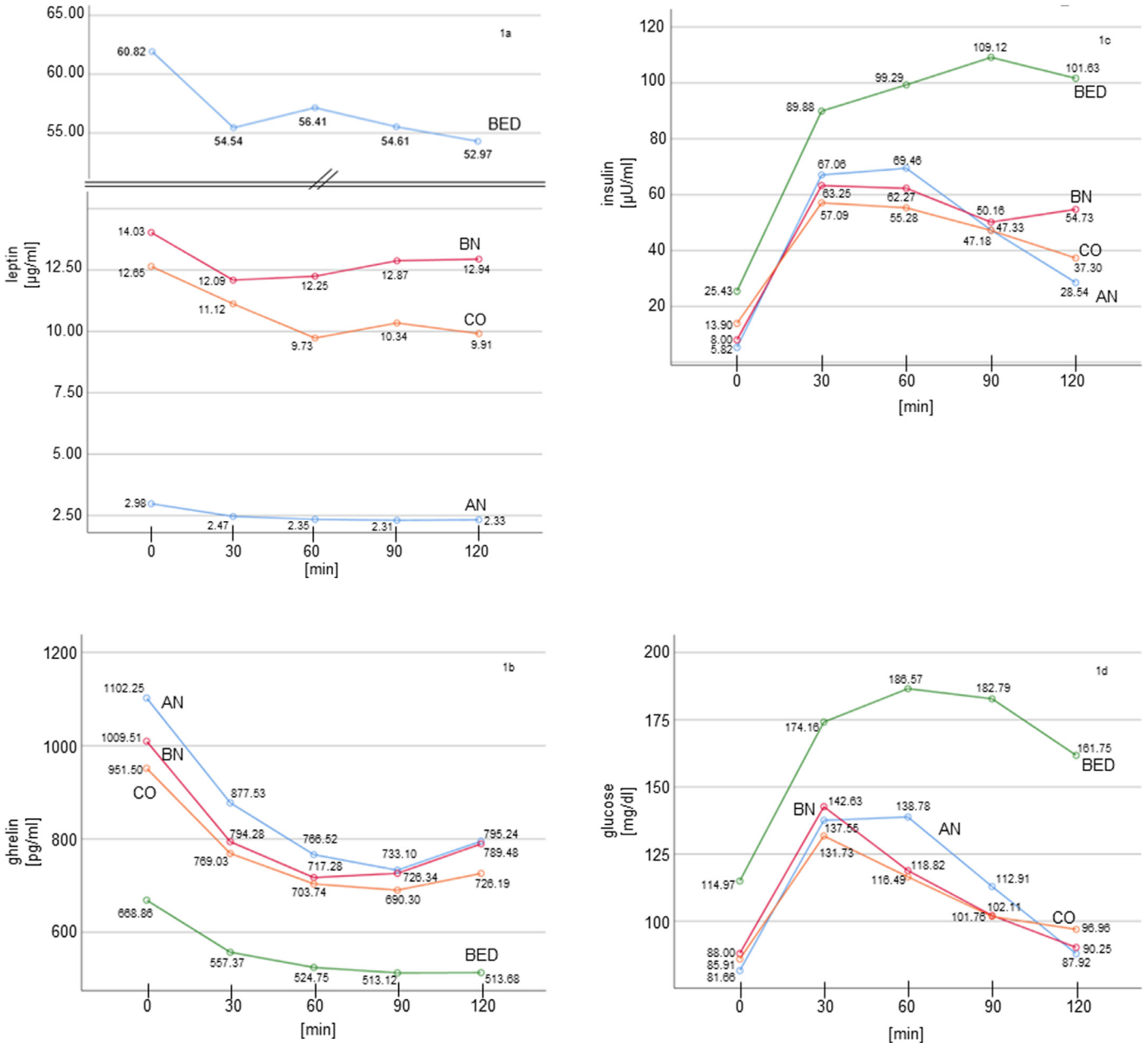

Fig. 1. The course of leptin (Fig. 1a), ghrelin (Fig. 1b), insulin (Fig. 1c), and glucose (Fig. 1d) concentrations during an OGTT (0, 30, 60, 90, 120 min.) in AN, BN, BED and CO. The AUCcorr. for leptin differed significantly between AN and CO ($p = 0.02$). OGTT = oral glucose tolerance test, AUCcorr. = area under the curve corrected for baseline concentrations.

have led to the implementation of functional tests to detect differences in secretion patterns. Research has transcended beyond the identification of changes in basal hormonal concentrations, toward the identification of mechanisms linking the hormonal dysfunction with ED symptomatology. Thus, an increasing number of studies have investigated hormonal secretion patterns in the context of feeding paradigms, stress paradigms, and behavioral tasks (e.g., attention bias or emotion-based disinhibition) (Culbert et al., 2016).

While most previous studies have assessed baseline concentrations of appetite-regulating hormones in patients with EDs and controls (Prince et al., 2009), this study applied the OGTT to assess the dynamics of appetite-regulating hormones in response to the oral administration of 75 g of glucose. This procedure may provide insight into altered physiological circuits that may not have been reflected in the single baseline measures of the respective hormones. AUCs were employed as measures of the overall functionality of the hormonal systems and corrected for baseline concentrations, since we expected those to have a significant impact on the overall hormonal responses following the glucose-loading procedure. This is the first study to combine these biological parameters with behavioral measures of response inhibition using a combined set-shifting x inhibitory control experimental paradigm, a set-shifting variant of a standard go/no-go task procedure using ED-specific food vs. neutral stimuli.

Impaired set-shifting has been described as an endophenotype in AN (e.g., Holliday et al., 2005, Lang et al., 2014); impaired inhibitory control is a common finding in BN and BED (Wu et al., 2013). To date, the association between neuropsychological performance and biological (hormonal) parameters other than cortisol or gonadal hormones, has not been studied in patients with EDs. Hildebrandt et al. (2016) investigated the association between performance in an emotional go/no-go task using happy, disgusted, and neutral stimuli as well as androgen concentrations; they found that patients with AN committed

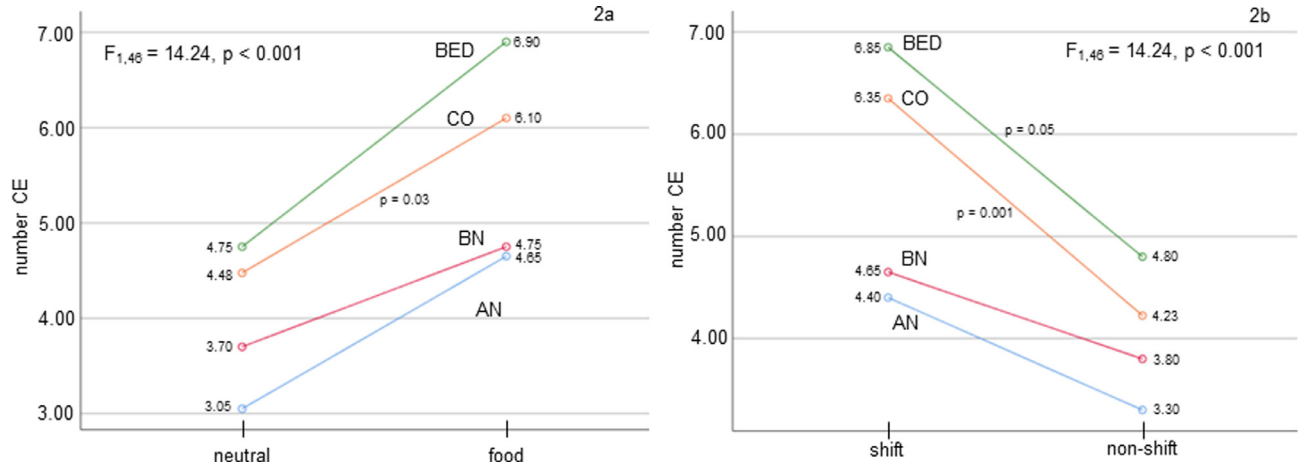

Fig. 2. The repeated measures ANOVA showed a main effect for category ($F_{1,46}$ = 14.24, p < 0.001; Fig. 2a) and for shift condition ($F_{1,46}$ = 20.71, p < 0.001; Fig. 2b), but no main effect for group. CE = commission errors.

significantly more CEs for happy and disgusted, as compared to neutral stimuli. Furthermore, testosterone was associated with decreased CE for patients with AN, but not associated with performance in healthy controls (Hildebrandt et al., 2016). Overall, not much is known about the interplay between appetite-regulating hormones and neuropsychological performance in ED patients. The association of appetite-regulating hormones with neuropsychological performance makes sense, considering that hormonal systems are intertwined. Low leptin levels are considered potentially responsible for the increased hypothalamus-pituitary-adrenal function in AN (Brambilla et al., 2003) and for amplifying the vicious circle of the hypothalamus-pituitary-gonadal axis dysregulation in AN patients owed to leptin's otherwise stimulatory effects on the gonadotropin-releasing hormone secretion (Comninos et al., 2014).

During the go/no-go task, participants were instructed to respond to a particular stimulus (go-run) and to inhibit responses to another stimulus (no-go run). Some studies have shown a higher total number of CE and omission errors (i.e., errors in response to the go stimuli) in AN (Seed et al., 2000), while others have shown that patients with AN only differ regarding a higher number of CEs and a shorter reaction latency, as compared to healthy controls (Butler and Montgomery, 2005). Another study reported that only patients with the binge-purging type, and not the restricting type, of AN differ in the number of total CEs, compared to controls; this is similar to patients with BN (Rosval et al., 2006). Our findings were more consistent with other studies, which have found no differences between ED patients and controls (e.g.,

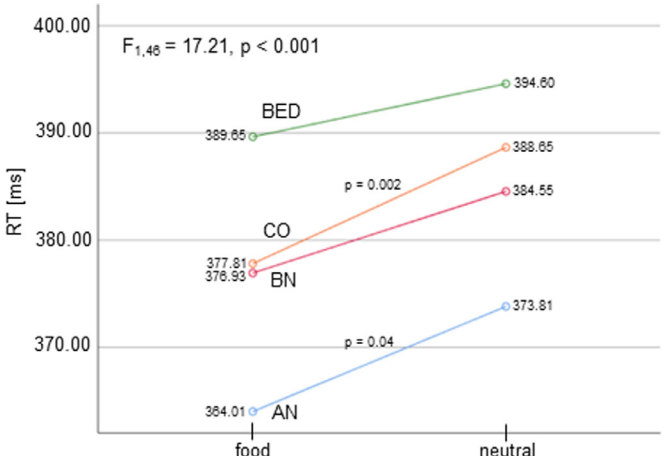

Fig. 3. The repeated measures ANOVA showed a main effect for category ($F_{1,46}$ = 17.21, p < 0.001), but no main effect for group. RT = reaction time.

Zakzanis et al., 2010, Lang et al., 2014). In the current study, most of the patients with AN (80%) were of the restricting type, which may help to explain the failure to observe differences. In addition, findings based on the WCST and the TMT provided no evidence of general impairment in set-shifting or executive function (e.g., due to malnutrition) in ED patients. Since some previous studies using food-specific go/no-go tasks

Table 2
Mean values ± standard deviations (SD) for commission errors (CE) and reaction times (RT, in seconds) in the food-specific go/no-go test in a set-shifting variant, such that the target category (food vs. neutral cues) differed in each block.

	mean ± SD	Group	mean ± SD	
CE in response to neutral cues and shift	3.50 ± 2.55	AN (n = 10)	369.45 ± 54.37	RT in response to neutral cues and shift
	4.30 ± 4.19	BN (n = 10)	384.47 ± 17.87	
	6.50 ± 3.78	BED (n = 10)	397.24 ± 24.52	
	5.55 ± 4.38	CO (n = 20)	386.46 ± 23.04	
CE in response to neutral cues and non-shift	2.60 ± 2.17	AN (n = 10)	378.18 ± 50.57	RT in response to neutral cues and non-shift
	3.10 ± 2.82	BN (n = 10)	384.62 ± 15.77	
	3.00 ± 2.79	BED (n = 10)	391.95 ± 20.15	
	3.40 ± 2.66	CO (n = 20)	390.84 ± 18.57	
CE in response to food cues and shift	5.30 ± 3.80	AN (n = 10)	361.62 ± 49.08	RT in response to food cues and shift
	5.00 ± 1.63	BN (n = 10)	376.37 ± 16.76	
	7.20 ± 2.30	BED (n = 10)	387.74 ± 22.33	
	7.15 ± 3.34	CO (n = 20)	378.49 ± 19.11	
CE in response to food cues and non-shift	4.00 ± 3.23	AN (n = 10)	366.40 ± 53.26	RT in response to food cues and non-shift
	4.50 ± 2.32	BN (n = 10)	377.50 ± 19.64	
	6.60 ± 4.74	BED (n = 10)	391.56 ± 22.04	
	5.05 ± 2.76	CO (n = 20)	377.13 ± 14.73	

Table 3
The table shows mean values ± standard deviations (SD) for each of the examined groups (AN, BN, BED, CO) for the WCST (Wisconsin Card Sorting Test) and the TMT (Trail Making Test, expressed as the ratio of TMT B to TMT A). For details, please refer to the main text.

	Group	mean ± SD	statistics
WCST total errors	AN (n = 10)	17.30 ± 11.04	MANOVA: $F_{12,114.06} = 2.16$, $\boldsymbol{p = 0.02}$, Wilks $\Lambda = 0.58$, partial $\eta^2 = 0.17$
	BN (n = 10)	10.20 ± 3.12	
	BED (n = 10)	16.00 ± 11.45	
	CO (n = 20)	9.70 ± 3.64	
WCST perserverations	AN (n = 10)	8.10 ± 4.43	
	BN (n = 10)	6.70 ± 2.79	
	BED (n = 10)	10.70 ± 10.06	
	CO (n = 20)	7.60 ± 3.53	
WCST perseverative errors	AN (n = 10)	7.20 ± 4.08	
	BN (n = 10)	5.20 ± 2.20	
	BED (n = 10)	8.60 ± 7.90	
	CO (n = 20)	5.75 ± 2.57	
WCSTcards to complete first category	AN (n = 10)	23.30 ± 17.13	
	BN (n = 10)	11.70 ± 2.06	
	BED (n = 10)	19.00 ± 16.60	
	CO (n = 20)	12.45 ± 3.56	
TMT B/A	AN (n = 10)	2.11 ± 0.87	ANOVA: $F_{3,46} = 1.21$; $p = 0.32$, partial $\eta^2 = 0.07$
	BN (n = 10)	1.71 ± 0.37	
	BED (n = 10)	1.90 ± 0.67	
	CO (n = 20)	1.73 ± 0.38	

have shown that obese patients with BED performed more poorly than both non-obese BED patients and normal-weight controls (Mobbs et al., 2011), our BED sample included only patients who were also obese. Obesity itself has been proposed as a predisposing factor for impaired performance. In a study by Calvo et al. (2014), using a non-specific (not food-related) go/no-go task, obese participants had slower RTs than lean participants. Similar to the current findings, CE in the go/no-go test did not differ between the obese and lean participants in Calvo et al. (2014) study. The methodological differences among various studies may account for the discrepant results. Task sensitivity might be affected by the type of stimuli used (e.g., words in the study by Mobbs et al. (2011) vs. pictures in the present study), technical task parameters, participants' hedonic mindset, or being on a weight-reducing diet; the slower RT could reflect to practical limitations related to body size in obese individuals.

Overall, findings regarding inhibitory control deficits in BED and/or obesity have been ambiguous. In their systematic review, Kittel et al. (2015) described no differences in inhibitory control between obese individuals and patients with BED when using neutral stimuli. Obesity was associated with inhibitory control deficits, independent of BED presence, in Lavagnino et al. (2016) meta-analysis. In another systematic review, Giel et al. (2017) similarly indicated that inhibitory impairments might not be related specifically to BED, but also to obesity. In contrast, using disorder-specific stimuli, Kittel et al. (2015) found that patients with BED showed greater inhibition deficits, as compared to obese individuals or normal-weight controls. In addition, when comparing obese patients with BED to patients with BED alone using food-specific stimuli, greater impairments in inhibitory control were found in obese patients with BED (e.g., Schag et al., 2013, Svaldi et al., 2014, Hege et al., 2015). Food-specific inhibitory control impairments have been proposed as a mechanism for binge eating episodes in BN and BED (e.g., Pearson et al., 2015, Turton et al., 2017). However, other studies have found no differences between obese patients with BED and those with BED alone (e.g., Svaldi et al., 2015, Kittel et al., 2017), and have not found differences that were not food-specific (Manasse et al., 2016). The inconsistency in findings may indicate that inhibitory control is more complex and influenced by several factors that have not been systematically assessed; e.g., negative emotions and emotion regulation deficits (Manasse et al., 2016, Leehr et al., 2018) or automatic processing as a putative moderator in the relationship between inhibitory control and eating behavior (Manasse et al., 2015; van Malderen et al., 2018). The use of different constructs and measures to assess inhibitory control makes it difficult to draw firm conclusions about its contribution to eating behaviors (Smith et al., 2018).

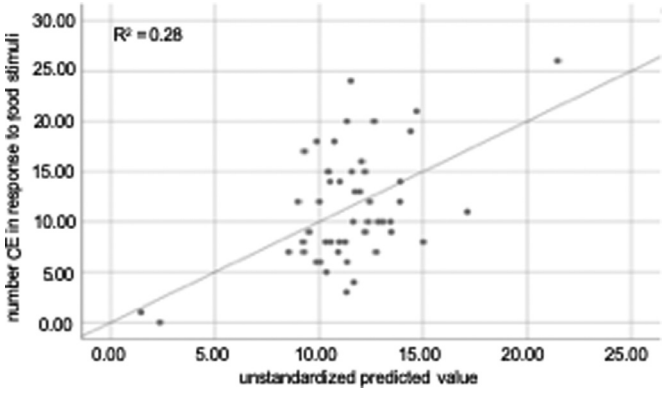

Fig. 4. A stepwise multiple linear regression was performed with RT to food-related stimuli entered as the control variable and group, AUCcorr. for leptin, and the group by AUCcorr. for leptin interaction as the predictor variables ($F_{2,47} = 8.92$, $p = 0.001$, $R^2 = 0.28$). The scatter plot depicts the multiple regression model R^2 value. Unstandardized predicted values were created based on the regression equation to predict the dependent variable commission errors CE. AUCcorr. = area under the curve corrected for baseline concentrations, RT = reaction time.

Table 4
Predictive capacity for commission errors (CE) in response to food cues in a stepwise linear regression. RT = reaction times, AUCcorr. = area under the curve corrected for baseline.

	Regression coefficient B	Standard Error	Beta	T	p	95% Confidence Interval Lower	Upper
RT food	2.22	0.70	0.40	3.17	**0.003**	0.81	3.63
$AUC_{corr.}$ leptin	1.82	0.70	0.32	2.60	**0.01**	0.41	3.23

Although preliminary in nature, our results may point toward a putative association between leptin responsivity and a core aspect of neuropsychological performance, such as inhibitory control. While patients with AN, as mentioned above, did not differ in their CE in response to food vs. neutral stimuli despite significantly faster RTs to food, it could be speculated that the lower net leptin concentrations in AN would act somewhat protectively against impulsive behavior. It is not possible to draw conclusions about underlying patho-mechanisms related to direct or mediating influences of leptin on neuropsychological performance; however, ED-specific psychopathology scores assessed in this study were not associated with the leptin secretion patterns. Existing studies related to the role of high vs. low leptin concentrations in impulsivity are discrepant. In one study, low leptin levels were associated with higher impulsivity, as assessed by the behavioral inhibition scale (BIS) in patients with a borderline personality disorder (Atmaca et al., 2002). In another study, Sutin et al. (2013) found that individuals high in self-discipline had lower peripheral leptin concentrations, while those with high impulsivity had higher levels of leptin. Nonetheless, it seems leptin not only exerts effects on metabolism, body weight, and fat storage, but on several other domains, including protection from cognitive decline in non-obese humans (e.g., McGuire and Ishii, 2016). There are studies that claim the neuroplasticity within the human brain partly depends on leptin (Dalamaga et al., 2013), although there are also discrepant findings showing no associations (Xing et al., 2015). Further supporting the notion of a relationship between leptin and cognitive performance, abnormally high leptin concentrations have been associated with poor academic performance in high school students (Correa-Burrows et al., 2016) and with poorer performance in the TMT-B in older adults (Gunstadt et al., 2008); conversely, low leptin levels have been associated with mild cognitive impairment in patients with type 2 diabetes (Yin et al., 2018). Since peripheral hormone levels do not mirror concentrations in the central nervous system, the effects of leptin require further elucidation.

5. Limitations

Limitations of this study include the small number of participants in each group and the resulting limited power to detect differences. However, curves for CEs and RTs in the go/no-go task were remarkably parallel, which might indicate similar results even with a greater number of participants. Another explanation for the failure to detect differences between groups in neuropsychological performance might relate to the significance of mood status on inhibitory control (e.g., Loeber et al., 2018). The groups under investigation may indeed not differ in their inhibitory control or set-shifting abilities under mood-indifferent laboratory conditions but may display performance differences when in an affective state e.g., sad, angry, or shameful (Giel et al., 2012; Paslakis et al., 2017). Differences in the net hormonal responses for leptin between AN patients and controls appear to be robust despite the small number of participants. Other appetite-regulating hormones and cortisol were not included in the study. In addition, other potentially confounding variables that could have affected our results, such as diabetes mellitus, menstrual phase, or the intake of estrogens, were not controlled. Since there were no differences between groups with regard to performance in the go/no-go test, the influence of concurrent depression appears unlikely. Besides, since this is a cross-sectional study, only the longitudinal data would be able to detect the normalization of hormonal responses in subsequent OGTTs or the lack of the same, as well as be able to examine the interdependence between the normalization of hormonal responses and the neuropsychological performance.

6. Conclusions

In summary, we investigated the concentrations of the appetite-regulating hormones ghrelin, leptin, insulin, and glucose in a functional manner, using the OGTT, and their association with neuropsychological performance in a pilot study of ED patients and controls. The primary finding was that the AUC for leptin, corrected for baseline concentrations, differed significantly between AN patients and controls and predicted performance in response inhibition, as indicated by the numbers of CEs in response to food stimuli in a set-shifting go/no-go task. Although the sample size was small, this study provides a clear rationale for conducting a larger study. Further investigation of the role of leptin in impulsive behavior in eating disorders is warranted.

Declaration of interest

The authors declare that they have no conflict of interest.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.psychres.2019.05.001.

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