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Associations between neuropsychological performance and appetite-regulating hormones in patients with anorexia nervosa and healthy controls: ghrelin´s putative role as a mediator of decision-making

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Abstract

Anorexia nervosa (AN) is a severe eating disorder accompanied by alterations in endocrinological circuits and deficits in neuropsychological performance. In this study, a series of appetite-regulating hormones (ghrelin, leptin, cholecystokinin, PYY, adiponectin, and visfatin) were measured under fasting conditions in female patients with AN and female healthy controls. All of the participants also underwent a battery of neuropsychological assessment [namely the Iowa Gambling Task (IGT), the Wisconsin Card Sorting Test (WCST), and the Stroop Color and Word Test (SCWT)]. As the main finding, we found that higher ghrelin levels predict better performance in the IGT. Ghrelin may be a putative mediator of decision-making, a finding that has not been described so far. The role of ghrelin in decision-making can only be described as speculative, as there are hardly any additional evidence-based data published up to date. Further studies are warranted.

Keywords: anorexia nervosa; ghrelin; appetite regulation; neuropsychological performance; decision-making

1. Introduction

Anorexia nervosa (AN) is characterized by restrictive eating patterns and fear of gaining weight (APA, 2013). ~~Despite the presence of strong physiological signals, e.g., hunger, patients with AN are capable of suppressing food intake. As a result of a high behavioral control regarding food intake on the one hand, and physical activity on the other, mostly leading to serious underweight,~~ Multi-level sequelae in terms of severe mental and somatic comorbidities are found among patients with AN (Schaumberg et al., 2017; Monteleone et al., 2018). The lack of energy availability due to the drastically reduced food intake in ~~patients with~~ AN leads to the disruption of physiological hormone signaling in several axes, e.g., the hypothalamus-pituitary-gonadal axis, while at the same time compensatory mechanisms set in to maintain homeostasis (Estour et al., 2010; Müller et al., 2009). ~~Estrogen deficiency and amenorrhea caused by impaired gonadotropin-releasing hormone secretion (Berga, 2001) and hypercortisolemia serving to sustain euglycemia (Estour et al., 2010) are well-established findings in AN.~~ Disturbed appetite-regulating circuits in AN have been repeatedly shown and have been reviewed elsewhere (Baskaran et al., 2017; Schorr and Miller, 2017; Tortorella et al., 2014). As a core finding, fasting plasma concentrations of the orexigenic peptide ghrelin are raised in underweight patients with AN and tend to normalize parallel to the progressive increase in weight during disorder-specific treatments (Monteleone et al., 2008; Otto et al., 2005). The concentrations of leptin, the principal regulator to decrease food intake and increase energy expenditure, are lower than normal in the plasma and the cerebrospinal fluid of patients with AN and also recover along with the recovery of body weight (Monteleone et al., 2008; Haas et al., 2018). ~~Additional dysregulated central and peripheral modulators of appetite in patients with AN have been extensively reviewed by Tortorella et al. (Tortorella et al., 2014). Changes in appetite-regulating hormones have been suggested to represent not only homeostatic adaptations to an altered energy balance, but to also determine the acquisition and/or maintenance of undernutrition, which may possess rewarding properties for patients (Monteleone and Maj, 2013; Monteleone et al., 2018).~~

Additionally, there is evidence for neuropsychological impairments in several cognitive domains in patients with AN compared to healthy controls (HC) (Aloi et al., 2015; Fassino et al., 2002; Roberts et al., 2013; Smith et al., 2018; Stedal et al., 2012; Wilsdon and Wade, 2006).

Increased cognitive control and inflexibility have been held accountable for the rigidity and compulsiveness of the eating behaviors exhibited by patients with AN. In neuropsychological studies, so-called set-shifting paradigms -with set-shifting being the ability to shift thoughts and actions depending on the context and most commonly assessed by the perseverative errors in the Wisconsin Card Sorting Test (WCST; Heaton et al., 1993)- may assess aspects of cognitive flexibility. Set-shifting abilities appear impaired among patients with AN (Fagundo et al., 2012; Holliday et al., 2005; Lang et al., 2014; Steward et al., 2016; Westwood et al., 2016). Next to poor set shifting, weak central coherence and difficulties in social-emotional processing have been proposed as endophenotypes in AN (e.g., Harrison et al., 2011; Holliday et al., 2005; Lang et al., 2014; Oldershaw et al., 2011; Roberts et al., 2013). Deficits in decision-making, captured in paradigms such as the Iowa Gambling Task (IGT; Bechara et al., 1997) are also present in AN (Tenconi et al., 2015; Fagundo et al., 2012; Guillaume et al., 2015; Perpiñá et al., 2017; Giannunzio et al., 2018; Steward et al., 2016). ~~Discounting long-term consequences, patients with AN tend to prefer immediate rewards (Tchanturia et al., 2012).~~ Decision-making deficits have been found to be prognostically decisive (Cavedini et al., 2006).

Inferences between neuroendocrine signaling and neuropsychological performances have been scarcely published, especially in patients with eating disorders (ED). Impaired neuropsychological performance has been linked to hormonal alterations regarding cortisol and estrogen in AN (e.g., Buehren et al., 2011; Chui et al., 2008; Sherwin, 2007). There is hardly evidence associating neuropsychological performance in patients with AN with hormones other than cortisol or estrogen. Hildebrandt et al. investigated the association between performance in an emotional go/no-go task using happy, disgust, and neutral cues and androgen concentrations; the authors found that patients with AN committed significantly more commission errors for happy and disgust cues, as compared to neutral cues. The same authors also showed that testosterone was associated with decreased commission errors for patients with AN, but was not associated with the performance in healthy controls (Hildebrandt et al., 2016). Little is also known regarding the interplay between appetite-regulating hormones and neuropsychological performance in patients with AN (Misra and Klibanski, 2014). The association of appetite-regulating hormones with neuropsychological performance makes sense considering that hormonal axes are intertwined; low leptin concentrations are held potentially

responsible for the increased hypothalamus-pituitary-adrenal function in AN (Brambilla et al., 2003), and for boosting the vicious circle of hypothalamus-pituitary-gonadal axis dysregulation in patients with AN, due to leptin´s otherwise stimulatory effects on the gonadotropin-releasing hormone secretion (Comninos et al., 2014).

In the present study, we assessed both neuropsychological performance as well as fasting concentrations of appetite-regulating hormones in female patients with AN and healthy female controls. We aimed at examining whether hormonal concentrations would be associated with performance in a series of neuropsychological tests. However, due to the lack of current evidence regarding inferences between appetite-regulating hormones and neuropsychological performance in eating disorders, ~~while at the same time there are conflicting results regarding the associations between endocrine responses and cognitive performance in clinical cohorts other than those with eating disorders,~~ no specific hypotheses linking specific hormones with specific cognitive tests could be defined a priori.

2. Materials and Methods

2.1 Cohort recruitment

The total sample comprised N = 157 participants; N = 51 female patients with AN [34 patients with restrictive AN (AN-R) and 17 patients with binge/purge AN (AN-BP)], and N = 106 healthy controls (HC). All participants were female, aged between 18 and 60 years and spoke Spanish as their first language. Patients with AN were consecutively referred for assessment and treatment at the Eating Disorders Unit within the Department of Psychiatry at the Bellvitge University Hospital in Barcelona, Spain. Mean age at onset of AN were 20.8 years (SD = 8.2 years) and mean duration of the eating disorder were 7.3 years (SD = 6.3 years). All patients with AN were diagnosed according to the DSM-5 diagnostic criteria (APA, 2013) by experienced clinicians specialized in the treatment of eating disorders. Healthy controls were recruited through several sources including word-of-mouth and advertisements at the local university.

The exclusion criteria in the sample included: a) history of chronic medical illness or neurological condition that might have affected cognitive function, b) head trauma with loss of

consciousness for more than 2 min, learning disability or mental retardation, c) use of psycho-active medications or drugs, d) male sex, e) age under 18 or over 60 years (to omit age-associated neuropsychological deficits), and f) previous history of ED in the HC group.

2.2 Instruments

2.2.1 Iowa Gambling Task (IGT) (Bechara et al., 1997)

This computer task evaluates decision-making, risk, reward and punishment value. Participants are asked to select 100 cards from four decks (A, B, C and D). After each card selection feedback is provided, with gain or loss of money. Decks A and B are not beneficial as the final loss they bring is higher than the final gain. Decks C and D, however, are linked to smaller losses and are thus the advantageous ones. The objective of the IGT is to gain as much money as possible. The score is calculated by subtracting the amount of cards chosen from decks A and B from the amount of cards chosen from decks C and D.

2.2.2 Wisconsin Card Sorting Test (WCST) (Heaton et al., 1993)

The WCST is an established measure of cognitive flexibility, i.e., the ability to shift between stimuli. Participants are asked to match a target card with one of four category cards displaying different shapes (triangle, star, cross and circle) of different colors (red, green, yellow, or blue shapes) and in different numbers (one, two, three or four shapes). The target card might be matched by shape, color, or number according to a classification rule only known by the experimentator. After each trial a feedback is given to the participant, indicating if the target card has been matched correctly. During the task, the experimentator changes the classification rule in an unpredicted manner and participants are then challenged to identify the new pattern and match accordingly. The test ends when the participant has managed to complete 6 categories or 128 trials.

2.2.3 Stroop Color and Word Test (SCWT; Golden, 1978)

The SCWT assesses interference (inhibition) control, flexibility and attention. In its paper and pencil form it includes three pages: a page with color words printed in black ink; a page with many “X’’ printed in color ink; a page with names of colors printed in an incongruent color (i.e.,

the word ‘‘green’’ printed in blue ink). Participants are asked to read as many words as possible from the first page in 45 seconds; then, they are asked to name the color of the ink on pages 2 and 3. Three scores (number of words on page 1, number of color-named ‘‘X’’ on page 2, and number of color-named words on page 3) as well as an additional ‘‘interference score’’ are obtained. Higher scores in the SCWT are indicative of a higher capacity of inhibition response.

2.2.4 Eating Disorders Inventory-2 (EDI-2) (Garner, 1991).

This is a widely used self-report questionnaire for the evaluation of several eating disorder-associated traits. It contains 64 items belonging to eight subscales: drive for thinness, bulimia, body dissatisfaction, ineffectiveness, perfectionism, interpersonal distrust, interoceptive awareness and maturity fears. Twenty seven additional items form three further subscales: asceticism, impulse regulation, and social insecurity. Each item is answered on a 6-point Likert scale and the total sum-score is available as a global measure of severity. The EDI-2 was validated in Spanish (Garner, 1998).

2.2.5 The Dutch Eating Behavior Questionnaire (DEBQ; van Strien et al., 1986)

The DEBQ consists of 33 items with 5 response options (from ‘‘never’’ to ‘‘very often’’) assessing three eating styles: emotional eating (13 items), external eating (10 items) and restrained eating (10 items). The average score on each subscale is also the final score on that subscale. The Spanish version of this instrument was validated by Cebolla et al. (Cebolla et al., 2014).

All of the above mentioned self-report questionnaires used in the study obtained excellent internal consistency in the sample (Cronbach’s alpha values α are included in Table 1 below).

2.3 Laboratory analyses

Blood samples from all participants were collected after a 12 hours fast into blood collection tubes with a serum separator. Tubes were centrifuged at 4000 r.p.m. at room temperature. The serum was separated and immediately frozen at -80 °C. Biochemical variables were measured in duplicate. Ghrelin levels were measured by means of an ELISA kit (Millipore Corporation,

Billerica, MA, USA). Leptin, adiponectin, cholecystokinin-33 (CCK-33) and peptide YY (3-36) were also measured by means of ELISA kits (BioVendor Research and Diagnostic Products, Laboratorni medicina a.s., Czech Republic). Visfatin levels were assessed by means of the ELISA kit from Phoenix Pharmaceuticals (California, USA).

All participants were informed about the procedures and gave their written informed consent. Procedures were approved by the Ethical Committee of the Bellvitge University Hospital.

2.4 Statistical analysis

Statistical analysis was carried out with Stata15 for windows. Comparison between the groups was based on chi-square tests (χ^2) for categorical variables and analysis of variance (ANOVA) for quantitative variables (the required conditions for the use of parametrical tests are met). Mean comparisons for the neuropsychological measures were adjusted for educational level (in years), and effect sizes for the mean differences were estimated using Cohen's-*d* coefficient (effect sizes were considered low-poor for $|d| > 0.20$, moderate-medium for $|d| > 0.5$ and large-high for $|d| > 0.8$; Kelley and Preacher, 2012). In addition, the Finner method, a familywise error rate stepwise procedure which offers more powerful tests than the classical Bonferroni correction, was used to control for type-I error due to multiple comparisons (Finner, 1993).

The associations between hormonal concentrations and neuropsychological as well as eating disorder-related measures were assessed by applying partial correlation estimates, adjusted for participants' age and educational level. Due to the strong association between statistical significance for the correlation estimates and sample size (low coefficients tended to be significant in a large sample size, while high coefficients tended to be non-significant in the case of small sample size), effect sizes were considered low-poor for $|R| > 0.10$, moderate-medium for $|R| > 0.24$ and large-high for $|R| > 0.37$; these thresholds correspond to Cohen's-*d* of 0.20, 0.50, and 0.80, respectively; Rosnow and Rosenthal, 1996).

Multiple linear regression was used to obtain predictive models for the main variables regarding the neuropsychological performance of the study participants (defined as outcomes), using a stepwise procedure to automatically select the significant predictors among a set of

independent variables including the participants' age, BMI, hormonal concentrations and eating disorder-related psychopathological profile (EDI-2 total and DEBQ scales).

Pathways analysis, a straightforward extension of multiple regression modeling, tested the underlying inference pattern between the study variables. In this work, path analysis was used as a case of structural equation modeling (SEM), which allows measuring mediational links, direct and indirect effects, defining the maximum-likelihood estimation method of parameter estimation and valuing goodness-of-fit using the standard statistical measures (Barrett, 2007; Bentler, 1990): non-significant result in the global χ^2 test, root mean square error of approximation RMSEA < 0.08, Bentler's Comparative Fit Index CFI > 0.90, Tucker-Lewis Index TLI > 0.90, and standardized root mean square residual SRMR < 0.10. The global predictive capacity of the model was measured by the coefficient of determination (CD). The dichotomous variable "group" was entered to the SEM coded as 0 = HC and 1 = AN.

3. Results

3.1 Cohort characteristics

Table 1 displays the cohort characteristics. Differences between the groups were obtained for education (higher levels in the HC subsample), while no differences were found in age. Regarding clinical variables, as expected, the means for the BMI and the DEBQ emotional and external scores were higher in the HC group, while the AN group achieved higher means in the EDI-2 total and the DEBQ restrained scales.

--- Insert Table 1 here ---

		Anorexia Nervosa (AN) N = 51		Healthy Controls (HC) N = 106				
	α	*Mean*	*SD*	*Mean*	*SD*	*F*	*df*	*p*
Age (years-old)		27.43	8.65	27.16	7.80	0.04	1/155	.844
Education (years)		14.69	2.86	16.93	2.75	22.44	1/155	**<.001***
BMI (kg/m^2)		17.44	1.63	21.73	2.85	99.35	1/155	**<.001***
EDI-2 Total score	0.960	78.78	43.28	25.42	20.21	111.28	1/155	**<.001***
DEBQ-restrained	0.952	34.16	12.80	21.70	7.66	57.68	1/155	**<.001***
DEBQ-emotional	0.953	23.31	11.69	27.65	9.57	6.10	1/155	**.015***
DEBQ-external	0.901	20.76	7.55	30.31	6.75	63.72	1/155	**<.001***

Table 1: Cohort characteristics.

SD: standard deviation. α: Cronbach's alpha in the sample.EDI-2 = Eating Disorder Inventory-2, DEBQ = Dutch Eating Behavior Questionnaire.

*Bold: significant parameter (0.05 level). †Effect size into the moderate (|*d*| > 0.50) to high range (|*d*| > 0.80).

The correlation matrix (partial correlation estimates adjusted for participants' age and educational level) between hormonal concentrations on the one hand and the neuropsychological and eating disorder-related measures on the other, stratified by group, are shown in Table S1 (supplementary material).

3.2 Group comparisons for baseline hormonal concentrations and neuropsychological performance

The upper half of Table 2 displays comparisons of mean concentrations of the hormones under investigation between AN and HC and shows significant differences for leptin (lower mean concentrations in the AN group) and adiponectin (higher mean concentrations in the AN group). The lower half of Table 2 displays comparisons of the applied neuropsychological measures

between the groups and shows a significantly better performance in the IGT for the HC group (higher mean in HC compared to AN), as well as in the WCST number of errors (lower mean in HC compared to AN) and the WCST conceptual (higher mean in HC compared to AN).

--- Insert Table 2 here ---

	Anorexia Nervosa (AN) N = 51		Healthy Controls (HC) N = 106		AN vs. HC	
	Mean	*SD*	*Mean*	*SD*	*p*	|*d*|
Hormones						
Ghrelin, pg/ml	748.39	359.16	719.01	272.27	0.673	0.09
Peptide YY, ng/ml	1.70	0.47	1.60	0.51	0.217	0.22
Cholecystokinin, pmol/l	1.41	0.49	1.57	0.59	0.097	0.29
Leptin, ng/ml	4.50	4.24	15.31	10.31	**<.001***	**1.37**†
Adiponectin, ng/ml	16.53	6.41	12.67	4.48	**<.001***	**0.70**†
Visfatin, ng/ml	8.43	3.60	7.42	3.21	0.077	0.30
[1]*Neuropsychology*						
IGT-1	-1.95	4.03	-1.74	6.98	0.857	0.04
IGT-2	0.35	4.23	2.99	8.20	**0.040***	0.40
IGT-3	0.61	5.14	5.33	8.42	**0.001***	**0.68**†
IGT-4	1.63	6.41	6.52	9.32	**0.002***	**0.61**†
IGT-5	1.79	8.88	4.86	10.41	0.088	0.32
IGT-Total	2.36	20.20	18.02	29.01	**0.001***	**0.63**†
WCST Trials	91.91	22.11	87.08	16.16	0.139	0.25
WCST Correct	65.68	11.76	67.76	7.69	0.218	0.21
WCST Errors	26.38	26.19	19.33	16.79	**0.049***	0.32
WCST Perseverative responses	14.47	19.41	10.56	8.55	0.094	0.26
WCST Perseverative errors	12.96	15.23	9.85	7.57	0.102	0.26
WCST Non-perseverative errors	13.34	16.29	9.48	10.01	0.087	0.29
WCST Conceptual	58.12	18.13	63.23	11.33	**0.045***	0.34
WCST Categories-completed	5.06	1.99	5.56	1.33	0.079	0.29
WCST Trials.Comp.1st.Category	22.12	30.07	19.32	23.64	0.544	0.10
Stroop Interference (SCWT)	7.12	7.88	4.69	6.93	0.068	0.33

Table 2: Comparison between the groups regarding hormone concentrations and neuropsychological performance. Blood samples from all participants were collected after a 12 hours fast.

[1]Results adjusted for education. SD: standard deviation. IGT-1 to -5 = Iowa Gambling Task runs 1 to 5, WCST = Wisconsin Card Sorting Test, SCWT = Stroop Color and Word Test.

*Bold: significant parameter (0.05 level). [†]Effect size into the moderate (|*d*| > 0.50) to high range (|*d*| > 0.80).

3.3 Predictive model for the neuropsychological performance

Table 3 includes the two multiple regressions performed in the study, for the IGT total and the stroop interference. Results showed that, when considering the whole sample, better performance in the IGT (higher scores) was related to higher BMI and higher ghrelin levels, while higher scores for stroop interference (i.e., better capacity of inhibition response) was related to lower age and lower BMI.

--- Insert Table 3 here ---

		B	SE	Beta	*p*	95% CI (B)		R^2
IGT-Total	BMI (kg/m^2)	0.733	0.333	0.181	**0.029***	0.075	1.391	0.060
	Ghrelin	0.007	0.003	0.163	**0.049***	0.000	0.014	
Stroop interference	Age (years)	-0.284	0.068	-0.314	**<.001***	-0.419	-0.150	0.143
	BMI (kg/m^2)	-0.391	0.170	-0.173	**0.023***	-0.728	-0.054	

Table 3: Predictive model for the neuropsychological profile in the total sample.

*Bold: significant parameter (0.05 level). Sample size: N = 157. IGT = Iowa Gambling Task.

3.4 Pathways analysis (SEM)

Figure 1 shows the path-diagram with the standardized coefficients obtained in the SEM. This is the final adjusted model after valuing the contribution of all hormones under investigation (a latent class was defined with the completed profile) and the neuropsychological performance (a latent class was also valued with all measures in the study). Since latent classes assessing hormones and neuropsychological performance only contained ghrelin and stroop interference as significant, it was only these two measures that were retained in the final model to allow better fitting. In the same line, a latent class with the eating disorder-related psychopathological measures was tested (labeled "ED-related psychopathology" in the path-diagram), which retained two significant variables (EDI-2 total and DEBQ restrained eating).

The final model, adjusted for the participants' educational level, achieved goodness-of-fit (χ^2 = 5.063, p = 0.281; RMSEA = 0.041; CFI = 0.994; TLI = 0.980; SRMR = 0.023) and a very good global predictive capacity (CD = 0.575). Worse psychopathological status (higher eating disorder severity and higher DEBQ restrained eating score) was directly related to lower levels in ghrelin and lower scores in the stroop interference, as well as affiliation to the AN group. An indirect effect was also found: patients with AN achieved higher scores in the stroop interference measure, which also contributed to psychopathology (i.e., stroop interference achieved a mediational role between diagnostic subtype and psychopathology).

--- Insert Figure 1 here ---

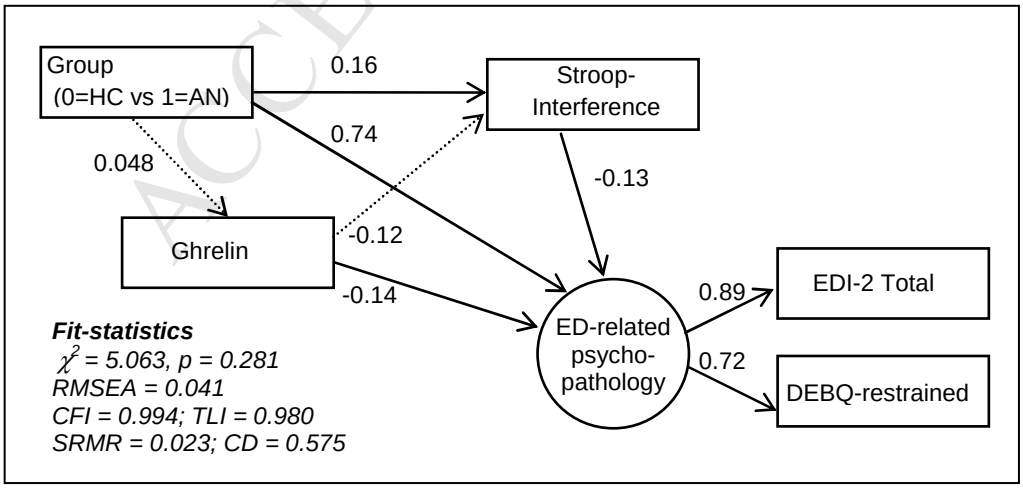

Figure 1: Path-diagram (SEM) with standardized coefficients. Continuous line: significant coefficient ($p \leq 0.05$). Dash line: non-significant parameter ($p > 0.05$). Sample size: N = 157. Results adjusted for the participants' educational level. ED-related psychopathology = Eating disorder-related psychopathology (mirrored by the total scores in EDI-2 and DEBQ). EDI-2 = Eating Disorder Inventory-2, DEBQ = Dutch Eating Behavior Questionnaire.

Direct, indirect and total effects of the SEM are displayed in Table S2 (supplementary material).

4. Discussion

In the present study, we examined executive functioning profiles (decision-making, cognitive flexibility, and response inhibition) in female patients with AN and female HC. At the same time, fasting concentrations of ghrelin, leptin, adiponectin, cholecystokinin-33 (CCK-33), peptide YY (3-36), and visfatin were measured. The aim of the study was to explore associations between the neuropsychological performances and the neuroendocrinological status of the participants.

As the main finding, patients with AN showed impaired neuropsychological performance compared to HC in the tests applied (IGT, WCST). These results are in concordance with previous findings (Tenconi et al., 2015; Fagundo et al., 2012; Perpiñá et al., 2017; Steward et al., 2016; Westwood et al., 2016). In contrast to HC, patients with AN are not able to select more advantageous over disadvantageous decks in the course of the IGT and choose immediate gains at the cost of more significant losses in the long run (Adoue et al., 2015; Bodell et al., 2014; Danner et al., 2012). ~~Performance in the IGT is linked in several studies to the activity of the orbitofrontal cortex (Bechara et al., 1999); interestingly, in patients with AN, significant volume decreases in the orbitofrontal cortex were associated with worse performance in the IGT (Bodell et al., 2014).~~ In a recent study, lower IGT scores were positively associated with a higher risk for developing AN (Na et al., 2019).

As the second main finding, we describe ghrelin as a putative predictor of decision-making, with higher ghrelin concentrations associated with better performance in the IGT, when considering patients with AN as well as HC. Although previous studies have associated neurocognitive performance, namely executive functions, with various peptides (e.g., endocannabinoids) in overweight and obesity (Bove et al., 2016; Fagundo et al., 2013; Labad et al., 2013; Miller et al., 2015), there is a lack of similar studies in eating disorders or AN (Galderisi et al., 2003). Based

on our results, we may speculate that high ghrelin levels could be considered somewhat protective against fails in decision-making, although high ghrelin levels in AN are not a sufficient precondition to prevent patients from erroneous performances in the IGT. As discussed further below, there is cumulating evidence showing that ghrelin-mediated signaling has an important role in cognitive performance (e.g., Chen et al., 2017). As far as the present finding is concerned, despite statistical significance, it is not yet possible to draw any firm conclusions regarding the clinical effects of ghrelin on the executive functions of patients with AN. Besides, executive functions in AN, e.g., decision-making, may be related to other factors that were not part of this investigation.

Finally, in the SEM analysis, there was an association between higher eating disorder-related psychopathology (i.e., higher scores for eating disorder severity and restrained eating) and both lower levels of ghrelin and poor inhibitory control in the group of patients with AN. Although no direct association was found between ghrelin concentrations and executive functioning impairment, our findings suggest that both variables may act as mediators in the pathogenesis of AN. According to our results, patients with AN and lower ghrelin levels seem to be more severely ill and display more impaired decision-making.

In a previous investigation (Chen et al., 2017), ghrelin levels were found to be positively associated with executive function in the WCST in patients with type 2 diabetes mellitus, and ghrelin has therefore been proposed as a possible new predictor of deficits in executive function in these patients. However, there are also studies showing results pointing towards a different direction. Higher ghrelin levels were linked to poorer cognitive performance in older non-demented adults (Spitznagel et al., 2010) and were also found to be associated with impulsivity (a surrogate of poor decision-making), in terms of lower self-control and higher tendency of acting without thinking in social drinkers (Ralevski et al., 2018). In the present study, no associations between ghrelin levels and performance in the WCST were found; thus, the different results between studies might be attributable to discrepancies in the role of ghrelin on neuropsychological performance depending on specific characteristics of the cohort under investigation. Cognitive rigidity in patients with AN has been deeply studied and corroborated (Fagundo et al., 2012); our results suggest that ghrelin has no influence on this lack of cognitive flexibility in patients with AN. Such single findings regarding the role of ghrelin on neurocognitive

performance are to be considered highly preliminary and certainly need to be verified in future investigations.

Nevertheless, a growing body of evidence supports the notion that ghrelin not only exerts effects on metabolism, body weight, and fat storage, but also has several other central effects (Anderberg et al., 2016, Carlini et al., 2008, Li et al., 2003). ~~In preclinical studies, the intracerebroventricular administration of ghrelin increased both motor and choice impulsivity in rats (Anderberg et al., 2016) and reversed deficits in object recognition memory in food-restricted female mice (Carlini et al., 2008). Ghrelin has also been associated with hippocampal proliferation and differentiation (Li et al., 2013). Further on,~~ Reward behavior for food is increased by ghrelin (Menzies et al., 2013; Skibicka et al., 2012). At the same time, food reward behavior has been shown to be associated with impulsivity (Velázquez-Sánchez et al., 2014). Our results did not display an association between ghrelin levels and inhibitory control in the SCWT in the regression model. Although both the IGT and the SCWT may assess aspects of the impulsivity construct, they may assess different aspects of it, i.e., impulsive choice (impulsive decision-making in the IGT) and (dis-)inhibition (in the case of the SCWT). Thus, it could be speculated that ghrelin in humans exerts a role in impulsive choice. Future longitudinal investigations of hormonal changes and changes in neuropsychological performance before and after disorder-specific treatment might help to elucidate to which extent normalization of ghrelin levels goes along with amelioration in decision-making in patients with AN.

~~It is still unclear to which degree neuropsychological impairments across eating disorders may be seen as etiopathogenetic or maintenance factors (Smith et al., 2018). In the study by Steward et al., performance in the IGT did not differ from HC in full-remitted patients with AN at a 1-year follow-up (Steward et al., 2016), suggesting that deficits in decision-making may be considered a state rather than a trait characteristic of AN (Steward et al., 2016). Conversely, deficits in decision-making have also been documented in the healthy relatives of patients with AN, suggesting that decision-making may be considered a trait, or even a further candidate intermediate phenotype of AN (Galimberti et al., 2012).~~

Our results may only be considered preliminary. Limitations of the study include the cross-sectional design that does not allow cause/effect conclusions. Moreover, we have only

assessed baseline concentrations rather than the functional dynamics of appetite-regulating hormones (e.g., in response to a standardized test meal or glucose ingestion); the latter could have probably captured inferences that were not captured by the present study design. We also studied general decision-making based on the IGT; future studies might investigate food intake-associated decision-making in patients suffering from AN. We also did not control for depression, which might have influenced results. Additionally, it must be considered that peripheral hormone levels by no means mirror concentrations in the CNS. Central nervous system effects thus remain to be further elucidated. Finally, our clinical cohort did not include severely underweight patients with AN, as we examined rather moderately ill patients attending day hospital treatment; thus, different results (e.g., stronger associations in the SEM or significance of other hormonal markers in the regression model, etc.) might have been the case in a cohort of severely ill patients with AN. Notwithstanding these limitations, the current study is, to our knowledge, the first study displaying a link between the appetite-regulating hormone ghrelin and decision-making in patients with AN and HC.

5. Conclusions

In conclusion, our findings suggest that ghrelin may play a putative role as a mediator of decision-making. ~~Research is moving beyond the mere identification of impairments (clinical phenotypes) and towards the identification of underlying pathomechanisms. Following this line,~~ An increasing number of studies have investigated hormone secretion patterns in the context of feeding paradigms, stress paradigms and behavioral tasks (e.g., attention bias, emotion-based disinhibition) (Culbert et al., 2016). Still, the role of appetite-regulating hormones within such contexts is far from being clear. The present study is the first one to point towards a possible role of ghrelin in decision-making, in terms that higher ghrelin concentrations are linked to better performance in the IGT, i.e., advantageous decision-making. At the same time, lower ghrelin levels are associated with higher ED-related psychopathology. While these findings require further replication and confirmation, they may encourage further research promoting the understanding of pathophysiological mechanisms linking hormonal dysfunction with neuropsychological deficits and ED-related psychopathology. Additionally, although there was

no direct relationship between ghrelin concentrations and inhibitory control, our results suggest that both these factors (i.e., lower ghrelin levels and poor inhibitory control) were associated with more severe eating disorder-related psychopathology, and, therefore, might act as mediators of the severity of the disorder in patients with AN.

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Highlights:

- There is evidence for neuropsychological impairments in several cognitive domains in patients with Anorexia Nervosa (AN) compared to healthy controls (HC), e.g., deficits in decision-making as assessed in the Iowa Gambling Task (IGT).
- The lack of energy availability due to the drastically reduced food intake in AN leads to the disruption of physiological hormone signaling in several axes. Fasting concentrations of the orexigenic peptide ghrelin are raised in underweight patients with AN and tend to normalize parallel to the progressive increase in weight during disorder-specific treatments.
- There is hardly evidence associating neuropsychological performance in patients with AN with hormones other than cortisol or estrogen, e.g., appetite-regulating hormones.
- In the present study, a series of appetite-regulating hormones (ghrelin, leptin, cholecystokinine, PYY, adiponectin, and visfatin) were measured under fasting conditions in female patients with AN and female HC. All of the participants also underwent a battery of neuropsychological assessment [namely the Iowa Gambling Task (IGT), the Wisconsin Card Sorting Test (WCST), and the Stroop Color and Word Test (SCWT)].
- As the main finding, we describe ghrelin as a putative predictor of decision-making, with higher ghrelin concentrations associated with better performance in the IGT, when considering patients with AN as well as HC. Our results add to the cumulating evidence showing that ghrelin-mediated signaling has an important role in cognitive performance.