

## Smell–taste dysfunctions in extreme weight/eating conditions: analysis of hormonal and psychological interactions

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**Abstract** (1) The objective of this study is to analyze differences in smell–taste capacity between females in extreme weight/eating conditions (EWC) and (2) to explore the interaction between smell/taste capacity, gastric hormones, eating behavior and body mass index (BMI). The sample comprised 239 females in EWC [64 Anorexia nervosa (AN) and 80 age-matched healthy-weight controls, and 59 obese and 36 age-matched healthy-weight controls]. Smell and taste assessments were performed through

“Sniffin’ Sticks” and “Taste Strips,” respectively. The assessment measures included the eating disorders inventory-2, the symptom check list 90-revised, and The Dutch Eating Behavior Questionnaire, as well as peptides from the gastrointestinal tract [Ghrelin, peptide YY, cholecystokinin]. Smell capacity was differentially associated across EWC groups. Smell was clearly impaired in obese participants and increased in AN (hyposmia in Obesity was 54.3 and 6.4 % in AN), but taste capacity did not vary across EWC. Ghrelin levels were significantly decreased in obese subjects and were related to smell impairment. EWC individuals showed a distinct smell profile and circulating ghrelin levels compared to controls. Smell capacity and

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ghrelin may act as moderators of emotional eating and BMI.

**Keywords** Anorexia nervosa · Smell · Taste · Obesity · Emotional eating · Ghrelin

## Introduction

Obesity (OB) and anorexia nervosa (AN) are two complex extreme weight/eating conditions (EWC) that are good examples of polarity in humans on a metabolic and behavioral continuum. EWC also share some phenotypical traits [1], including psychopathological variables [2–4] and specific environmental risk factors and biological vulnerabilities [5, 6]. However, AN and OB lie on opposite ends of this continuum with respect to food intake and dietary behaviors (i.e., undernutrition vs excess dietary intake, in AN and OB, respectively) may affect the functioning of the chemo-sensory system [7]. This is also the case of the sensorial system and its association with appetite, food preferences, and food intake [8]. However, whereas loss of smell (anosmia/hyposmia) and taste (ageusia/hypogeusia) are strongly associated with changes in the hedonic response to food and in weight fluctuations [7], little is known about how these sensorial systems function together in EWC individuals.

Very few studies have investigated smell and taste functions in AN, and they have produced contradictory results. While most studies showed some olfactory impairments in AN when compared with controls [7, 9, 10], others detected increased capacity [11, 12] or did not detect any olfactory dysfunction [13]. Furthermore, AN patients appear to have more deficits in taste capacity than controls [9], which is partially justified by altered brain activation [14], even after recovery [15].

Similarly, smell and taste functions in obesity have rarely been studied and contradictory results have also been found. Morbidly obese individuals were found to have lower smell capacity than moderately obese individuals [16], especially in odor detection and identification [17]. Regarding taste, in obese adults [18], an impaired capacity for sweet and salty food was found.

This variety of results might be partially due to methodological gaps (lack of sample power, the use of differential assessment procedures, and not having controlled relevant variables).

A number of recent studies have suggested that smell and taste capacity are also modulated by the endocrine system

apart from central regulation. Several gut hormones have been linked to the smell–taste capacity with ghrelin, peptide YY (PYY), and cholecystokinin (CCK) being the most representative. Thus, ghrelin seems to increase human sniffing response, peptide YY to modulate taste responsiveness, and CCK is a major agent in taste signaling. Additionally, interactions between gut hormones, sensory processing (taste and olfaction) and emotional regulation have been described [19]. In this line, a relevant role of prefrontal regions, mainly the orbitofrontal cortex, has been observed [19]. Results have suggested that circulating hormones reach the orbitofrontal cortex via cortical-hypothalamic circuits [20]. Concurrently, odor and taste information also arrives to the orbitofrontal cortex via the thalamus and somatosensory cortex [21]. Finally, the orbitofrontal cortex integrates this available information and gives a value to the food stimulus [19]. However, scarce data about the complex interface between these gut hormones and smell–taste capacity in EWC are available [22–25].

Therefore, the aims of this study were (1) to analyze differences in smell/taste capacity between female individuals in extreme eating/weight conditions; (2) to determine the prevalence of hyposmia/hypogeusia among the groups and to assess associations with other clinical variables; (3) to analyze whether smell/taste capacity is associated with clinical and psychopathological variables and peptides of gastrointestinal tract (i.e., PYY, Ghrelin, CCK); and (4) to analyze whether body mass index (BMI; kg/m<sup>2</sup>) is predicted by taste/smell capacity.

## Materials and methods

### Participants

The total sample comprised 239 individuals at the extremes of the BMI continuum [64 AN, and 80 age-matched healthy-weight controls (YHC), and 59 obese individuals (OB) and 36 age-matched healthy-weight controls (OHC)]. All participants were female and aged between 18 and 50 years. Within the entire AN sample, 43 patients were diagnosed with restrictive subtype (AN-R) and 21 with binge/purging subtype (AN-BP). Eating disorder (ED) diagnoses were made according to Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) [26] criteria, using a semi-structured clinical interview [27] conducted by experienced psychologists and psychiatrists. The mean age of ED onset was 18.6 years (SD = 4.6) and the mean duration of the disorder was 5.5 years (SD = 5.3). Participants reported a weekly average of 0.32 binge eating episodes (SD = 1.1) and 1.5 vomiting episodes (SD = 2.7).

Seven centers, all involved in the Spanish Biomedical Research Centre in Physiopathology of Obesity and

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Nutrition (CIBERObn), participated in the study. The AN and OB participants were patients who had been consecutively referred to the clinics mentioned above. Recruitment of the controls took place by means of word-of-mouth and advertisements at local universities. All controls were from the same catchment area as the clinical groups. Table 1 contains the descriptive information for the sample of participants: mean (and standard deviation) for quantitative features, percentages (%) for categorical variables and values for statistical comparisons between groups based on ANOVA for ordinal measures and  $\chi^2$  tests for categorical measures.

Exclusion criteria for all the participants were (a) having a history of chronic medical illness or neurological condition that might affect the smell–taste tests; (b) having used psychoactive medications or drugs that may interfere with smell–taste capacity or BMI; (c) being male (due to the low prevalence in AN); (d) being under 18 or over 50-year old; and (e) having any substance abuse/dependence. Additionally, in the healthy eating controls and obesity group, an additional exclusion criterion was having suffered a lifetime ED. Enrolment in the study was between January 2010 and March 2013. All participants gave written and signed informed consent and the Ethics Committee of all the institutions involved approved the study.

## Measures

A comprehensive assessment battery was administered which measured eating symptomatology and emotional/restrictive eating patterns, sociodemographic characteristics, and general psychopathology. Additionally, blood samples and anthropometrical data were collected from

participants. Besides medical and clinical relevant information, it was recorded number of cigarettes consumed/day, presence/absence of diabetes (type 1 and 2), and use of hormonal contraceptives.

## Psychometrical measures

### *The Eating Disorder Inventory-2 (EDI-2: [28])*

The EDI-2 is a reliable and valid multidimensional self-report questionnaire composed of 91 items assessing cognitive and behavioral characteristics that are typical in eating disorders. All of these scales are answered on a 6-point Likert scale, and provide standardized subscale scores. A validation in a Spanish population has shown a moderate mean internal consistency of  $\alpha = 0.63$ .

### *The Symptom Checklist-90 Revised (SCL-90-R: [29])*

The SCL-90-R is a widely used 90-item scale for assessing self-reported psychological distress and psychopathology. The test is usually scored on nine primary symptom dimensions. In the current study, only the depression scale was considered. This scale has been validated in the Spanish population obtaining a Cronbach's alpha coefficient of 0.75.

### *The Dutch Eating Behavior Questionnaire (DEBQ; [30])*

It is composed of 33 items with 5 response choices (from “never” to “very often”) measuring three eating styles: emotional eating, external eating, and restrained eating. This questionnaire has been shown to have good reliability and convergent validity. The Cronbach's alpha in the

**Table 1** Descriptives for sample

	AN ( <i>n</i> = 64)	YHC ( <i>n</i> = 80)	OHC ( <i>n</i> = 36)	OB ( <i>n</i> = 59)	<i>p</i> <sup>a</sup>
Age (years); mean (standard deviation)	24.0 (5.3)	22.6 (2.9)	37.3 (5.9)	37.5 (8.7)	<.001
Employment status; % employed	32.1	39.7	77.1	46.3	<.001
Use of hormonal contraceptives (%)	28.1	28.8	16.7	11.9	0.059
Smoking (%)	26.6	25.0	36.1	20.3	0.339
Body mass index (current); mean (SD)	17.4 (1.4)	21.6 (2.9)	22.4 (2.6)	42.7 (6.6)	<.001
Fat mass (kg)	7.2 (3.0)	15.6 (5.6)	16.6 (5.1)	51.6 (12.8)	<.001
Fat-free mass (kg)	39.7 (3.7)	43.7 (4.1)	43.6 (4.4)	61.9 (7.8)	<.001
TBW (%)	28.7 (3.0)	31.5 (2.9)	31.2 (3.2)	44.4 (5.6)	<.001
EDI-2-total score	71.8 (41.5)	26.4 (19.0)	22.7 (23.7)	77.7 (33.8)	<.001
SCL-90-R depression; mean (SD)	1.91 (1.0)	0.67 (0.5)	0.63 (0.5)	1.57 (0.9)	<.001

TBW total body water (%), AN anorexia, YHC young healthy controls, OHC old healthy controls, OB obese, EDI-2 eating disorders inventory-2. SCL90-R

<sup>a</sup> *p* based on  $\chi^2$  test for categorical descriptive and ANOVA for quantitative

current sample is 0.95 for emotional eating, 0.89 for external eating, and 0.94 for restrained eating.

### Smell and taste assessments

#### *Sniffin' sticks* [31, 32]

Smell testing was performed using “Sniffin' Sticks.” This includes subtests for the odor threshold, odor discrimination, and odor identification. The test consists of felt-tip pen-like odor dispensers (sticks). All of them ranged between 0 and 16. Three odor categories are identified: Odor threshold (OT), Odor discrimination (OD), and odor identification (OI). In OT subtest, the higher the score, the greater the smell capacity. The sum of the scores from the three subtests resulted in the TDI-score (Threshold, Discrimination, and Identification) with a maximum of 48 points. As defined in previous report [33], a score of 30.5 points or more indicates normosmia, a score between 16.5 and 30 points indicates reduced smell function in terms of hyposmia, and a score of less than 16.5 points indicates a smell functional impairment or anosmia.

#### *Taste strips* [34]

The “Taste strips” test consists of 16 taste impregnated filter papers of a length of 8 cm with a tip area of 2 cm<sup>2</sup>. Each of the 16 taste strips is impregnated with one of these four tastings: sweet, sour, salty, and bitter. The following concentrations were used for the taste strips: sweet: 0.4, 0.2, 0.1, 0.05 g/ml sucrose; sour: 0.3, 0.165, 0.09, 0.05 g/ml citric acid; salty: 0.25, 0.1, 0.04, 0.016 g/ml sodium chloride; and bitter: 0.006, 0.0024, 0.0009, 0.0004 g/ml quinine hydrochloride. The strips were placed on the left and right sides of the anterior third of the extended tongue. Before each administration of a strip, the mouth was rinsed with water. Normogeusia was defined as a test score of nine and higher, while a score below nine was considered a sign of hypogeusia [34].

### Analysis of endocrine parameters

Blood samples from all the subjects were collected after a 12-h fast into blood collection tubes with a serum separator. After 15 min, tubes were centrifuged at 4000 r.p.m. at room temperature. The serum was separated and immediately frozen at −80 °C. Plasma biochemical variables were measured in duplicate. Ghrelin levels were measured by ELISA kit (Millipore Corporation, Billerica, MA, USA). Cholecystokinin-33 (CCK-33) and peptide YY (3–36) were measured by ELISA kits (BioVendor Research and Diagnostic Products, Laboratorni medicina a.s., Czech Republic).

### Anthropometric measures

Body composition (i.e., BMI, fat mass, fat-free mass, and total body water) was assessed using the Tanita Multi-Frequency Body Composition Analyzer MC-180MA (Tanita Corporation, Tokyo, Japan). Height was calculated using a stadiometer.

### Procedure

Experienced psychologists-psychiatrists and physicians completed the clinical and psychometrical assessment in two-structured face-to-face interviews. Prior to assessment, basic anthropometrical features and body composition were measured, and blood samples were obtained after overnight fasting. The first interview provided information about current eating disorder symptoms, antecedents, and other clinical and health data of interest. In addition to the first clinical interview, eating/psychopathological information was obtained through self-report questionnaires. During the second interview, for the smell–taste assessment, individuals were requested not to smoke, chew gum, or having eaten any products during the previous 60 min.

### Statistical analysis

Statistical analyses were carried out with SPSS20 and Stata13 for Windows. Differences in taste–smell, eating style, and hormonal factors between diagnosis subtypes were valued with analysis of variance (ANOVA) adjusted to covariates age, SCL-90-R depression subscale, use of tobacco, the presence of diabetes and use of hormonal contraceptives. Post hoc comparisons (through Fisher's least significance difference, LSD, procedure) estimated mean differences between diagnosis conditions.

Binary logistic regressions, also adjusted in the previous covariates, compared the prevalence for hyposmia and hypogeusia between diagnostic subtypes. Multiple regressions in three steps/blocks examined the predictive contribution of smell–test total scoring and hormonal and eating style (predictors) on the BMI (criterion). First step/block included the covariates age, SCL-90-R depression, use of tobacco, and use of hormonal contraceptives. Second step/block added smell–test total scoring. Third step/block included the hormonal measures and the DEBQ score. The change increase in  $R^2$  coefficient ( $\Delta R^2$ ) measured the incremental-specific predictive capacity of each step/block compared to the previous. The mediational hypotheses were tested through Structural Equation Models (SEM, with Stata13 system). Goodness-of-fit was considered adequate for [35] non-significant result in the  $\chi^2$  test ( $p > 0.05$ ), the Root Mean Squared Error of Approximation (RMSEA) lower than 0.08, baseline comparison

indexes (Comparative Fit Index—CFI- and Tucker-Lewis Index—TLI-) higher than 0.90 and residuals size measured through Standardized Mean Squared Residual (SRMR) lower than 0.08. Coefficient of determination (CD) measured the predictivity capacity ( $R^2$ ) for the global model.

## Results

### Smell-taste capacity between EWC

Table 2 contains the results of the ANOVA comparing the smell–taste measures between diagnoses, adjusted for age, depression, smoking and contraceptive use. The first columns include descriptions for each diagnostic condition (adjusted means and SD), followed by the significance test for the global mean comparison (F-statistic) and the pairwise comparisons (contrasts, post hoc comparisons). Statistical differences emerged for most of the smell capacity measures, namely odor threshold (AN achieved higher mean scores than the other three groups, and OB obtained lower means than OHC) (see Online Resource-Figure S1), odor identification (OB obtained the lowest mean scores compared with the other three groups), and TDI-score (OB registered a lower mean score than AN and OHC). Regarding gustatory capacity, the mean for sweet taste was lower for AN compared to YHC, and the sour taste mean was lower for OB compared to OHC.

In the AN subsample, a stepwise multiple regression selected the best predictors of the odor-threshold identification levels considering the age of onset, duration of the disorder, BMI, SCL-90R scores, EDI-2 scores, DEBQ

scores, and hormone levels (see Online Resource-Table S1) as potential predictors. A final model showed that higher odor threshold scores were associated with higher age of onset, higher BMI, higher SCL-90 depression, lower EDI-2 body dissatisfaction/bulimia/impulse regulation scores, higher EDI-2 perfectionism, higher DEBQ-restrained, higher PYY levels, and lower CCK values.

Table 3 includes estimated prevalence (95 % confidence interval) for the presence of hyposmia and hypogeusia for each diagnostic condition. The second part of the table includes the results from two logistic regressions considering hyposmia and hypogeusia as criteria; subtype as an independent variable; and patients' age, depression, smoking, and use of contraceptives as covariates. Results show that the prevalence of hypogeusia did not differ between diagnostic groups, range of 18.0 % for AN, 21.4 % for OB, 9.3 % for OHC and 14.4 % for YHC. With regards to hyposmia, prevalence was in the range of 6.4 % for AN, 23.6 % for OHC, 33.0 % for YHC, and 54.3 % for OB, and significant statistical differences emerged comparing AN to OB and YHC.

### Eating styles and gastrointestinal tract hormones among EWC

The first columns of Table 4 include descriptive statistics (mean and SD) for DEBQ scores and hormonal levels. The following columns include ANOVA results, adjusted for age, depression, smoking, and the use of contraceptives, comparing the mean values between groups: F-statistic and pairwise comparisons (post hoc contrasts). The comparison of means of eating style and hormonal factors (adjusted to

**Table 2** Comparison of smell–taste for diagnostic subtypes: ANOVA adjusted by age, depression, smoking, and contraceptives

	Adjusted means and SE				Factor diagnosis		Pairwise (post hoc) comparisons					
	AN (n = 64)	YHC (n = 80)	OHC (n = 36)	OB (n = 59)	$F_{3,217}$	$p^a$	YHC vs AN	OHC vs AN	OB vs AN	OHC vs YHC	OB vs YHC	OB vs OHC
Odor threshold	8.78; 0.36	6.42; 0.30	7.14; 0.44	5.99; 0.35	14.77	<0.001	<b>2.36*</b>	<b>1.64*</b>	<b>2.79*</b>	−0.72	0.43	<b>1.15*</b>
Odor discrimination	13.0; 0.31	12.5; 0.26	13.2; 0.38	12.5; 0.31	1.968	0.120	0.49	−0.23	0.53	−0.72	0.03	0.76
Odor identification	13.0; 0.31	13.1; 0.26	12.8; 0.38	11.8; 0.31	3.368	<b>0.026</b>	−0.10	0.26	<b>1.20*</b>	0.36	<b>1.30*</b>	<b>0.94*</b>
TDI-score	34.8; 0.67	32.0; 0.56	33.1; 0.82	30.3; 0.66	9.994	<0.001	<b>2.75*</b>	1.67	<b>4.52*</b>	−1.08	1.77	<b>2.85*</b>
Taste strips sweet	3.10; 0.15	3.47; 0.13	3.58; 0.18	3.25; 0.15	1.820	0.241	− <b>0.37*</b>	−0.48	−0.15	−0.11	0.22	0.33
Taste strips sour	2.20; 0.16	2.37; 0.14	2.50; 0.20	1.94; 0.17	2.213	0.241	−0.17	−0.30	0.26	−0.13	0.43	<b>0.56*</b>
Taste strips salty	2.74; 0.19	2.85; 0.17	2.73; 0.23	2.46; 0.20	0.631	0.596	−0.11	0.01	0.28	0.11	0.39	0.27
Taste strips bitter	2.52; 0.20	2.89; 0.18	2.72; 0.25	2.65; 0.21	0.692	0.596	−0.37	−0.20	−0.13	0.17	0.24	0.07
Total “taste strips”	10.6; 0.46	11.6; 0.42	11.5; 0.57	10.3; 0.48	1.897	0.241	−1.02	−0.95	0.27	0.07	1.29	1.22

TDI sum of scores for threshold-discrimination-identification measures, AN anorexia, YHC young healthy controls, OHC old healthy controls, OB obese

\* Bold: significant coefficient (05 level)

<sup>a</sup>  $p$  value includes Bonferroni–Simes correction for multiple comparisons

**Table 3** Comparison of hypوسmia-hypogeusia among EWC groups

	Adjusted prevalences; second line: 95 % CI prev				Logistic regression adjusted by age, depression, smoking and contraceptives						
	AN (n = 64)		OHC (n = 36)		OB (n = 59)		Diagn		Contrasts: OR; p; second line 95 % CI for OR		
	YHC (n = 80)	OHC (n = 36)	OB (n = 59)	p <sup>1</sup>	YHC vs AN	OHC vs AN	OB vs AN	OC vs YC	OB vs YC	OB vs OC	
Hypوسmia	6.44 % 2.45 ÷ 15.0	33.0 % 23.2 ÷ 43.4	23.6 % 11.7 ÷ 38.1	54.3 % 41.7 ÷ 66.3	<b>&lt;0.001</b>	<b>5.63; .004*</b> 1.75 ÷ 18.1	3.37; .129 0.70 ÷ 16.1	<b>12.7; .001*</b> 3.53 ÷ 45.7	0.60; .414 0.18 ÷ 2.05	2.26; .139 0.77 ÷ 6.64	<b>3.77; .014*</b> 1.31 ÷ 10.9
Hypogeusia	18.0 % 9.88 ÷ 28.2	14.4 % 8.79 ÷ 24.4	9.33 % 4.41 ÷ 25.3	21.40 % 13.5 ÷ 34.1	0.494	0.69; .487 0.24 ÷ 1.97	0.42; .267 0.09 ÷ 1.94	1.06; .923 0.33 ÷ 3.46	0.61; .506 0.14 ÷ 2.60	1.54; .512 0.43 ÷ 5.56	2.51; .137 0.75 ÷ 8.44

AN anorexia, YHC young healthy controls, OHC old healthy controls, OB obese

\* Bold: significant coefficient (05 level). Hosmer–Lemeshow: p = .716 (model for hypوسmia) and p = 0.333 (model for hypogeusia). Total sample (n = 239)

age, depression, smoking, and contraceptives use) between diagnoses also achieved statistical differences (Table 4). All the DEBQ scores differed between groups: (a) mean for emotional score was lower for AN compared to OB and YHC, and for OHC compared to OB; (b) mean external score was lower for AN compared with the other three groups; and(c) mean restrained score was lower for YHC compared to AN and OB, being the higher score in AN and the lower in OB. Considering the hormonal factors, OB achieved the lowest means for ghrelin compared to the other three groups. Regarding gut hormones, no differences were found in CCK or PYY levels between groups. However, OB subjects showed significant much more decreased ghrelin levels compared to other three groups (293 OB vs 814 OHC vs 673.7 YHC vs 716 AN, p < 0,001).

**Predictive capacity of smell-taste, hormones and eating style on BMI**

Table 5 contains the sequential multiple regression (in three steps-blocks) analyzing the contribution of smell-taste, hormones factors, and DEBQ-emotional scores on BMI: (a) the first step included the covariates of the study: patients’ age, depression, smoking, and use of contraceptives, explaining R<sup>2</sup> = 33.5 % of BMI variance; (b) the second block added smell-threshold-discrimination-identification level and taste total variables, which explained R<sup>2</sup> = 7.9 % of BMI variance; and (c) the third step added hormones levels and DEBQ-emotional scores, which added R<sup>2</sup> = 15.9 % to the explanation of the BMI variability. Results of the last step show that when controlled for age, depression, smoking, and contraceptives use, BMI was increased in older aged participants, higher scores on the smell scale, lower levels in ghrelin, and higher scores in the DEBQ-emotional eating score. Smell-taste measures explained 7.9 % of BMI variability and hormones, and DEBQ-emotional score explained 15.9 %.

**Structural SEM model: BMI and sensorial-behavioral-hormonal interactions**

SEM included in Fig. 1 shows the pathways of associations between the main variables of the study and BMI (standardized coefficients are reported in this figure). Ghrelin was included into the final model due that this hormone was strongly related to the other variables into the model (PPY and CCK were not considered into the model because they were not statistically related with the other measures into the pathway, and the inclusion of these both variables made worse fitting indexes). Smell and taste were decreased with older ages. Smell total score was negatively related to DEBQ-emotional score and taste total score was positively related to ghrelin hormone. As low the ghrelin

**Table 4** Comparison of eating style and hormonal factors: ANOVA adjusted by age, depression, smoking, and contraceptives

	Adjusted means and SE				Factor diagnosis		Pairwise (post hoc) comparisons					
	AN (n = 64)	YHC (n = 80)	OHC (n = 36)	OB (n = 59)	$F_{3,217}$	$p^a$	YHC vs AN	OHC vs AN	OB vs AN	OHC vs YHC	OB vs YHC	OB vs OHC
DEBQ- emotional	21.87; 1.88	30.82; 1.55	26.32; 2.27	34.11; 1.86	10.77	<.001	<b>8.96*</b>	4.45	<b>12.24*</b>	-4.51	3.28	<b>7.79*</b>
DEBQ- external	21.09; 1.19	30.98; 0.99	30.70; 1.44	30.63; 1.17	17.26	<.001	<b>9.89*</b>	<b>9.61*</b>	<b>9.54*</b>	-0.28	-0.35	-0.07
DEBQ- restrained	30.55; 1.48	22.22; 1.23	25.72; 1.78	28.78; 1.44	7.39	<.001	<b>-8.33*</b>	-4.83	-1.77	3.50	<b>6.56*</b>	3.06
PYY	1.67; 0.10	1.64; 0.08	1.52; 0.10	1.70; 0.09	0.85	0.700	-0.04	-0.16	0.03	-0.12	0.07	0.19
Ghrelin	716.6; 65.8	673.7; 52.9	814.3; 67.0	293.0; 60.1	17.50	<.001	-42.94	97.71	<b>-423.6*</b>	140.6	<b>-380.7*</b>	<b>-521.3*</b>
CCK	1.43; 0.10	1.52; 0.08	1.52; 0.10	1.56; 0.09	0.36	0.784	0.09	0.09	0.13	0.00	0.04	0.04

DEBQ Dutch Eating Behavior Questionnaire, PYY peptide YY, CCK Cholecystokinin, AN anorexia, YHC young healthy controls, OHC old healthy controls, OB obese

\* Bold: significant coefficient (05 level)

<sup>a</sup>  $p$ -value includes Bonferroni–Simes correction for multiple comparisons

concentration, as high the DEBQ-emotional eating score and the BMI were. In short, the BMI was directly associated to ghrelin (negative relationship), DEBQ-emotional eating and age (positive relationship in both cases). DEBQ-emotional score was a mediator factor into the association between ghrelin and BMI, and ghrelin was itself a mediator variable between taste total score and BMI. Goodness-of-fit was very good, and the predictive capacity for the global model was high ( $R^2 = 0.326$ ).

## Discussion

The first main finding of our study was that smell capacity was differentially associated across EWC groups. Olfaction was clearly impaired in obese participants (namely in threshold, identification, and total scores) and increased in AN. Accordingly, while the prevalence of hyposmia in obesity was 54.3 %, in AN it was only 6.4 %. Moreover, along with the negative association between smell capacity and BMI in the total sample, our most striking finding is that ghrelin levels are significantly reduced in obese subjects compared to AN or controls, and that this reduction is negatively and independently related to smell capacity.

It has previously been noted that gut hormones may alter the perception and pleasantness of specific odors, presumably either directly through their receptors in the olfactory system or indirectly through central interfaces between olfaction regulation systems, appetite control, memory and motivation [36]. Specifically, ghrelin, an appetite-

stimulating hormone produced primarily by the stomach, induces hunger, stimulates food intake, and enhances the pleasantness of meals [37]. A number of studies have shown not only that circulating ghrelin levels are decreased in human obesity [38] but also that morbidly obese individuals have lower smell capacity than moderately obese individuals [16], and that impairment in odor detection and identification also exists in overweight individuals [17]. However, scarce are the studies addressing the concrete nexus between ghrelin levels and smell capacity in EWC, and here is where our study adds significant knowledge.

Although in our clinical samples, it is not possible to distinguish whether these are state or trait findings, they may suggest that food-olfactory driven behaviors are clearly affected by the long-term metabolic status. In concordance with this potential explanation, recently in animal models, these findings were also replicated and found that smell capacity was diminished after hyperlipidemic diet [39]. This dysfunctional smell capacity in obese patients was even perpetuated after bariatric surgery and weight reduction [40]. Therefore, we may argue that in obesity, smell function might be a simple consequence of abnormal eating and extreme weight. However, this finding is open to other alternative explanations. In animal studies, olfactory bulb ablation induces overfeeding and consequently weight increases, indicating that smell impairment in obesity might not be just a consequence but a precursor of abnormal feeding and obesity. However, this alternative explanation may need a prospective design and it could not be tested in our study.

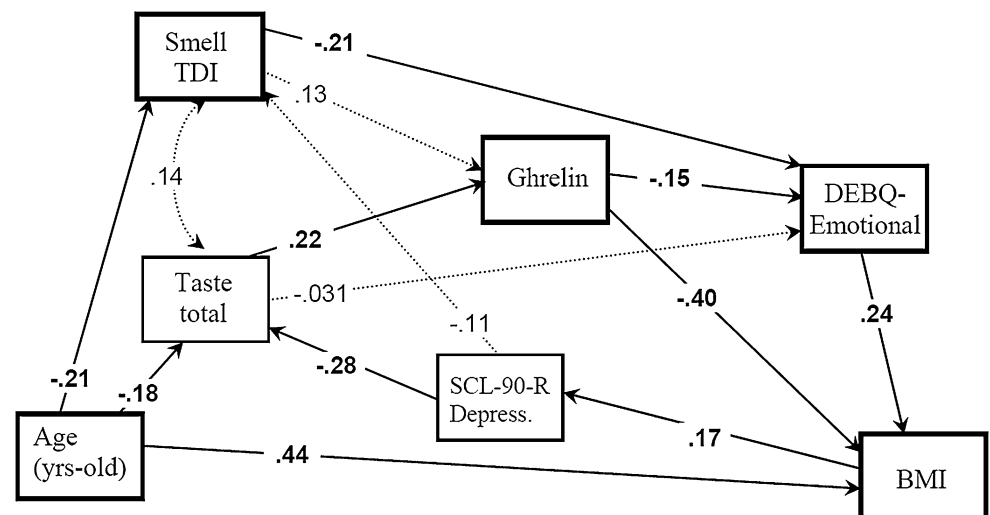
**Table 5** Multiple regression valuing the predictive capacity of smell–taste, hormones, and DEBQ-emotional on BMI

Criterion: body mass index (kg/m <sup>2</sup> )	B	SE(B)	Beta	p	95 % CI (for B)
First step: covariates					
Age	0.650	0.079	0.535	<.001	0.495; 0.805
SCL-90-R: depression	2.489	0.820	0.195	0.003	0.869; 4.108
Smoking	0.497	1.600	0.020	0.757	−2.663; 3.656
Contraceptives use	−0.632	1.622	−0.026	0.697	−3.835; 2.571
$\Delta R^2 = .335; p < .001$					
Second step: smell–taste					
Age	0.580	0.076	0.478	<.001	0.430; 0.730
SCL-90-R: depression	1.861	0.804	0.146	0.022	0.272; 3.449
Smoking	0.479	1.515	0.020	0.752	−2.513; 3.471
Contraceptives use	−0.315	1.538	−0.013	0.838	−3.352; 2.722
Smell: TDI	5.789	1.425	0.250	<.001	2.974; 8.604
Taste: total	3.881	1.942	0.127	0.047	0.046; 7.715
$\Delta R^2 = .079; p = .001$					
Third step: hormones, DEBQ-emotional					
Age	0.483	0.067	0.398	<.001	0.350; 0.616
SCL-90-R: depression	0.966	0.723	0.076	0.184	−0.463; 2.394
Smoking	0.249	1.319	0.010	0.850	−2.355; 2.854
Contraceptives use	−0.605	1.343	−0.024	0.653	−3.258; 2.048
Smell: TDI	3.896	1.268	0.168	0.003	1.391; 6.402
Taste: total	1.623	1.721	0.053	0.347	−1.776; 5.022
PYY	1.127	1.447	0.050	0.437	−1.731; 3.984
Ghrelin	−0.010	0.002	−0.351	<.001	−0.014; −0.007
CCK	−1.339	1.449	−0.059	0.357	−4.202; 1.523
DEBQ-emotional	0.175	0.052	0.190	0.001	0.072; 0.277
$\Delta R^2 = 0.159; p < .001$					

$\Delta R^2$ : increase/change in  $R^2$  for the step-block. Total sample ( $n = 239$ )

DEBQ Dutch Eating Behavior Questionnaire, PYY peptide YY, CCK Cholecystokinin, Smell-TDI (Sniffin' Sticks: Threshold-Discrimination-Identification)

**Fig. 1** Pathway analysis. Pathway valuing the association between smell-TDI (Sniffin' Sticks: Threshold-Discrimination-Identification), taste, ghrelin, DEBQ-emotional (Dutch Eating Behavior Questionnaire-emotional eating subscale), and body mass index (BMI) (controlled to age and depression score). *Dashline* non-significant association



$\chi^2=15.48$  ( $p=0.06$ ); RMSEA=0.07; CFI=0.96; TLI=0.90; SRMR=0.04; CD=0.326



On the other hand, anorexia nervosa patients showed a greater smell capacity when compared with controls and obese. This is an interesting result that was only partially described so far in the literature. Although impaired smell capacity has previously been identified in AN [7, 9, 10], only few studies detected increased capacity in AN when compared to controls [11, 12] in agreement with our findings. These contradictory results in the ED literature are basically due to methodological gaps in previous studies (not having controlled relevant variables, lack of sample power) and differential assessment procedures used. In our study, one of the largest sample so far on smell and taste capacity for AN, greater smell capacity (namely odor threshold) was found to be an indirect indicator of ED severity. In concordance with our findings, recent studies have found that 24 h fasting can induce smell capacity in humans [41]. Moreover, no changes in olfactory function have been described after treatment and weight recovery in AN [42], suggesting that greater smell capacity is independent of malnutrition and abnormal eating behaviors [11]. Again, prospective design studies are here needed in order to demonstrate whether altered smell capacity is consequence of starvation or a trait. It is important to note that observed values in healthy controls included in the study were similar to those obtained in the general population in Spain [43], which reinforces the consistency of our results.

The second main finding of the present report was that gustatory capacity did not vary across the extremes of EWC, with similar values of hypogeusia (ranging from 9.3 to 21.4 % among EWC groups). Hence, although prior studies found associations between undernutrition [44] or vomiting episodes [45] and hypogeusia, suggesting a direct effect of the acidic vomitus on the taste receptors located in the mouth, our findings were not able to find any influence of vomiting on this chemo-sensory system. The only two tastes found to be impaired were a lower sweet detection (only statistically significant in AN) and lower sour detection (only statistically significant in obesity). The first results agree with recently published studies showing that AN patients process taste stimuli differently than controls, especially regarding neural activation patterns when confronted with sweet stimuli [14], even after recovery [15]. Whether this lack of response to sweet in AN, may reflect an altered disgust processing [46], a starvation's sensorial consequence or a perceptual respond to sweet (e.g., alliesthesia effect), could not be answered in this study and should be further researched. The second one, the finding that obesity showed lower detection of sour stimuli, is in concordance with previous studies, where obese subjects identified some taste qualities less precisely than non-obese subjects [18]. As suggested recently in animals [47], mice under high fat diet had reduced ability to detect some taste

stimuli and may cause changes in the central taste system and taste perception.

The third main finding in the current study was that smell capacity (partially also taste) and ghrelin seem to act as contrasting mediators of eating behavior and predict BMI. Low smell function is associated with emotional eating with the consequent increase in BMI, as we have found in our obese patients. An additional relevant finding of this study is the decreased concentration of ghrelin in obesity, directly related to the decreased smell capacity. Limited data about these findings had been previously published and were limited by the small numbers of patients and lack of homogeneity [36]. Also prior studies reported that increased ghrelin in AN patients could subserve improved odor threshold, suggesting this can be impaired by undernutrition-induced peripheral neuropathy [12]. However, our results were not able to find significantly higher levels of this hormone in AN than in controls. Hence, it is unclear whether alterations in smell are related to starvation or malnutrition. The role of metabolic hormones in the sensory and regulatory aspects of energy homeostasis has been described in the literature [48, 49]. Accordingly, the interaction between olfaction, gut hormones and eating behavior has also been described in the literature regarding metabolic disorders (such as obesity and anorexia nervosa) [23]. In EWC, both cases this loop in interaction with a dysfunctional rewarding circuitry, as suggested by some authors [14], could further promote abnormal eating behavior and contribute to relapse.

### Limitations

Although the current study addresses a number of methodological gaps in the literature by controlling important potential confounders, there are limitations to consider. First, the current study was conducted solely with female participants because of the small number of male AN patients. Thus, it is unclear whether these findings could be generalized to men. Future studies should also assess male participants and their smell–taste capacity and whether they also showed similar smell dysfunctions and the interaction patterns found in our study. Secondly, the hormonal profile considered in the study is limited and may expand in future studies to other new hormonal compounds and targets that might be associated and partially explain the linkage between smell capacity–eating behavior and brain reward system in abnormal eating behaviors. Thirdly, although the sample considered was one of the largest samples where smell–taste capacity has been analyzed in AN and obesity so far, when compared with healthy eating/weight controls, the cross-sectional nature of the study does not allow us to determine causality, and it is unclear whether smell dysfunction in obese patients is a

consequence or a cause of abnormal nutritional and metabolic patterns. An important step for the future is to conduct longitudinal analyses on the association between smell capacity and hormonal compounds, on eating patterns and BMI, in EWC and to consider brain responses in order to expand the lacking information on the interaction between sensorial, hormonal, behavioral and brain responses.

Despite the limitations mentioned above, this study has several important strengths, including the significant sample size and the statistical path analysis used in this study (structural equation modeling, SEM) that allow us to include mediational associations among several related variables. The results obtained constitute empirical evidence for the development of further theories about the role of sensorial, hormonal, and eating patterns on extreme BMI.

## Conclusions

Our study provides further understanding of the pathophysiological underlying mechanisms of abnormal eating behavior and the interacting involvement of the sensorial system, gut hormones, hedonic eating, and BMI. Thus, we show that EWC individuals have dysfunctional smell capacity (characterized by hyposmia in obesity and increased smell capacity in anorexia nervosa), but preserved taste function. We also demonstrate not only that ghrelin concentrations are decreased in obesity, but also that reduced ghrelin concentrations are directly related to smell impairment in obese subjects. Finally, smell capacity in conjunction with peripheral ghrelin concentrations seems to act as contrasting mediators of eating behavior and consequent predictors of BMI.

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## Compliance with Ethical Standards

**Conflict of interest** The authors declare that they have no conflict of interest associated with this manuscript.

**Human and Animal Rights and Informed Consent** All procedures performed were in accordance with the ethical standards of the Ethics Committee of all the institutions involved and with the 1964 Helsinki Declaration and its later amendments. Informed consent was obtained from all individual participants included in the study.

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