Fernández-Aranda F, Agüera Z, Fernández-García JC, Garrido-Sanchez L, Alcaide-Torres J, Tinahones FJ, Giner-Bartolomé C, Baños RM, Botella C, Cebolla A, de la Torre R, Fernádez-Real JM, Ortega FJ, Frühbeck G, Gómez-Ambrosi J, Granero R, Islam MA, Jiménez-Murcia S, Tárrega S, Menchón JM, Fagundo AB, Sancho C, Estivill X, Treasure J, Casanueva FF. (2016). Smell–taste dysfunctions in extreme weight/eating conditions: analysis of hormonal and psychological interactions. *Endocrine, 51(2),* 256-267. doi: 10.1007/s12020-015-0684-9

Abstract

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 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 ametabolic 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 systemand 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/m2) is predicted by taste/smell capacity.

Method

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 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 v2 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 selfreport 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 a = 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 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 cm2. 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 R2 coefficient (DR2) 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 v2 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 (R2) 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 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 R2 = 33.5 % of BMI variance; (b) the second block added smell-threshold-discrimination-identification level and taste total variables, which explained R2 = 7.9 % of BMI variance; and (c) the third step added hormones levels and DEBQ-emotional scores, which added R2 = 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 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). DEBQemotional 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 (R2 = 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 appetitestimulating 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.

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.

References

1. A.B. Fagundo, R. de la Torre, S. Jime´nez-Murcia, Z. Agu¨era, R. Granero, S. Ta´rrega, C. Botella, R. Ban˜os, J.M. Ferna´ndez-Real, R. Rodrı´guez, L. Forcano, G. Fru¨hbeck, J. Go´mez-Ambrosi, F.J. Tinahones, J.C. Ferna´ndez-Garcı´a, F.F. Casanueva, F. Ferna´ndez-Aranda, Executive functions profile in extreme eating/weight conditions: from anorexia nervosa to obesity. PLoS ONE 7, e43382 (2012)

2. L. Claes, F. Ferna´ndez-Aranda, S. Jimenez-Murcia, C. Botella, F.F. Casanueva, R. de la Torre, J.M. Ferna´ndez-Real, G. Fru¨hbeck, F.J. Tinahones, N. Vilarrasa, M. Montserrat-Gil de Bernabe ´, R. Granero, Z. Agu¨era, C. Sancho, J. Muehlenkamp, J.M. Mencho´n, Co-occurrence of non-suicidal self-injury and impulsivity in extreme weight conditions. Personal. Individ. Differ. 54, 137–140 (2013)

3. C. Villarejo, S. Jime´nez-Murcia, E. A ´ lvarez-Moya, R. Granero, E. Penelo, J. Treasure, N. Vilarrasa, M. Gil-Montserrat De Bernabe ´, F.F. Casanueva, F.J. Tinahones, J.M. Ferna´ndez-Real, G.

Fru¨hbeck, R. De La Torre, C. Botella, Z. Agu¨era, J.M. Mencho˜n, F. Ferna´ndez-Aranda, Loss of control over eating: a description of the eating disorder/obesity spectrum in women. Eur. Eat. Disord. Rev. 22, 25–31 (2014)

4. C. Villarejo, F. Ferna´ndez-Aranda, S. Jime´nez-Murcia, E. Pen˜as-Lledo´, R. Granero, E. Penelo, F.J. Tinahones, C. Sancho, N. Vilarrasa, M. Montserrat-Gil de Bernabe´, F.F. Casanueva, J.M. Ferna´ndez-Real, G. Fru¨hbeck, R. De laTorre, J. Treasure, C. Botella, J.M. Mencho´n, F. Fernandez-Aranda, S. Jimenez-Murcia, E. Penas-Lledo, M. Montserrat-Gil de Bernabe, J.M. Fernandez-Real, G. Fruhbeck, J.M. Menchon, Lifetime obesity in patients with eating disorders: increasing prevalence, clinical and personality correlates. Eur. Eat. Disord. Rev 20, 250–254 (2012)

5. S. Jacquemont, A. Reymond, F. Zufferey, L. Harewood, R.G. Walters, Z. Kutalik, D. Martinet, Y. Shen, A. Valsesia, N.D. Beckmann, G. Thorleifsson, M. Belfiore, S. Bouquillon, D. Campion, N. de Leeuw, B.B. de Vries, T. Esko, B.A. Fernandez, F. Ferna´ndez-Aranda, J.M. Ferna´ndez-Real, M. Grataco`s, A. Guilmatre, J. Hoyer, M.R. Jarvelin, R.F. Kooy, A. Kurg, C. Le Caignec, K. Ma¨nnik, O.S. Platt, D. Sanlaville, M.M. Van Haelst, S. Villatoro Gomez, F. Walha, B.L. Wu, Y. Yu, A. Aboura, M.C. Addor, Y. Alembik, S.E. Antonarakis, B. Arveiler, M. Barth, N. Bednarek, F. Be´na, S. Bergmann, M. Beri, L. Bernardini, B. Blaumeiser, D. Bonneau, A. Bottani, O. Boute, H.G. Brunner, D. Cailley, P. Callier, J. Chiesa, J. Chrast, L. Coin, C. Coutton, J.M. Cuisset, J.C. Cuvellier, A. David, B. de Freminville, B. Delobel, M.A. Delrue, B. Demeer, D. Descamps, G. Didelot, K. Dieterich, V. Disciglio, M. Doco-Fenzy, S. Drunat, B. Duban-Bedu, C. Dubourg, J.S. El-Sayed Moustafa, P. Elliott, B.H. Faas, L. Faivre, A. Faudet, F. Fellmann, A. Ferrarini, R. Fisher, E. Flori, L. Forer, D. Gaillard, M. Gerard, C. Gieger, S. Gimelli, G. Gimelli, H.J. Grabe, A. Guichet, O. Guillin, A.L. Hartikainen, D. Heron, L. Hippolyte, M. Holder, G. Homuth, B. Isidor, S. Jaillard, Z. Jaros, S. Jime´nez-Murcia, G.J. Helas, P. Jonveaux, S. Kaksonen, B. Keren, A. Kloss-Brandsta¨tter, N.V. Knoers, D.A. Koolen, P.M. Kroisel, F. Kronenberg, A. Labalme, E. Landais, E. Lapi, V. Layet, S. Legallic, B. Leheup, B. Leube, S. Lewis, J. Lucas, K.D. MacDermot, P. Magnusson, C. Marshall, M. Mathieu-Dramard, M.I. McCarthy, T. Meitinger, M.A. Mencarelli, G. Merla, A. Moerman, V. Mooser, F. Morice-Picard, M. Mucciolo, M. Nauck, N.C. Ndiaye, A. Nordgren, L. Pasquier, F. Petit, R. Pfundt, G. Plessis, E. Rajcan-Separovic, G.P. Ramelli, A. Rauch, R. Ravazzolo, A. Reis, A. Renieri, C. Richart, J.S. Ried, C. Rieubland, W. Roberts, K.M. Roetzer, C. Rooryck, M. Rossi, E. Saemundsen, V. Satre, C. Schurmann, E. Sigurdsson, D.J. Stavropoulos, H. Stefansson, C. Tengstro¨m, U. Thorsteinsdo´ttir, F.J. Tinahones, R. Touraine, L. Valle´e, E. van Binsbergen, N. Van der Aa, C. Vincent-Delorme, S. Visvikis-Siest, P. Vollenweider, H. Vo¨lzke, A.T. Vulto-van Silfhout, G. Waeber, C. Wallgren-Pettersson, R.M. Witwicki, S. Zwolinksi, J. Andrieux,

X. Estivill, J.F. Gusella, O. Gustafsson, A. Metspalu, S.W. Scherer, K. Stefansson, A.I. Blakemore, J.S. Beckmann, P. Froguel, Mirror extreme BMI phenotypes associated with gene dosage at the chromosome 16p11.2 locus. Nature 478(7367), 97–102 (2011)

6. G.K.W. Frank, J.R. Reynolds, M.E. Shott, L. Jappe, T.T. Yang, J.R. Tregellas, R.C. O'Reilly, Anorexia nervosa and obesity are associated with opposite brain reward response. Neuropsychopharmacology. 37, 2031–2046 (2012)

7. K. Aschenbrenner, N. Scholze, P. Joraschky, T. Hummel, Gustatory and olfactory sensitivity in patients with anorexia and bulimia in the course of treatment. J. Psychiatr. Res. 43, 129–137 (2008)

8. K.J. Burdach, R.L. Doty, The effects of mouth movements, swallowing, and spitting on retronasal odor perception. Physiol. Behav. 41, 353–356 (1987)

9. F. Dazzi, S.De Nitto, G. Zambetti, C. Loriedo, A. Ciofalo, Alterations of the olfactory-gustatory functions in patients with eating disorders. Eur. Eat. Disord. Rev. 21, 382–385 (2013)

10. N. Rapps, K.E. Giel, E. So¨hngen, A. Salini, P. Enck, S.C. Bischoff, S. Zipfel, Olfactory deficits in patients with anorexia nervosa. Eur. Eat. Disord. Rev. 18, 385–389 (2010)

11. D. Stein, R. Gross-Isseroff, R. Besserglick, A. Ziv, G. Mayer, A. Yaroslavsky, A. Toledano, H. Voet, A. Weizman, H. Hermesh, Olfactory function and alternation learning in eating disorders. Eur. Neuropsychopharmacol. 22, 615–624 (2012)

12. G. Goldzak-Kunik, R. Friedman, M. Spitz, L. Sandler, M. Leshem, Intact sensory function in anorexia nervosa. Am. J. Clin. Nutr. 95, 272–282 (2012)

13. L.C. Kopala, K. Good, E.M. Goldner, C.L. Birmingham, Olfactory identification ability in anorexia nervosa. J. Psychiatry Neurosci. 20, 283–286 (1995)

14. G.K. Frank, M.E. Shott, J.O. Hagman, V.A. Mittal, Alterations in brain structures related to taste reward circuitry in ill and recovered anorexia nervosa and in bulimia nervosa. Am. J. Psychiatry 170, 1152–1160 (2013)

15. T.A. Oberndorfer, G.K.W. Frank, A.N. Simmons, A. Wagner, D. McCurdy, J.L. Fudge, T.T. Yang, M.P. Paulus, W.H. Kaye, Altered insula response to sweet taste processing after recovery from anorexia and bulimia nervosa. Am. J. Psychiatry 170, 1143–1151 (2013)

16. B.E. Richardson, E.A. Vander Woude, R. Sudan, J.S. Thompson, D.A. Leopold, Altered olfactory acuity in the morbidly obese. Obes. Surg. 14, 967–969 (2004)

17. U. Simchen, C. Koebnick, S. Hoyer, S. Issanchou, H.-J.F. Zunft, Odour and taste sensitivity is associated with body weight and extent of misreporting of body weight. Eur. J. Clin. Nutr. 60, 698–705 (2006)

18. F. Sartor, L.F. Donaldson, D.A. Markland, H. Loveday, M.J. Jackson, H.P. Kubis, Taste perception and implicit attitude toward sweet related to body mass index and soft drink supplementation. Appetite. 57, 237–246 (2011)

19. H.-R. Berthoud, C. Morrison, The Brain, Appetite, and Obesity. Annu. Rev. Psychol. 59, 55–92 (2008)

20. C.B. Saper, Hypothalamic connections with the cerebral cortex. Prog. Brain Res. 126, 39–48 (2000)

21. J.V. Verhagen, The neurocognitive bases of human multimodal food perception: consciousness. Brain Res. Rev. 53, 271–286 (2007)

22. M.S.La Sala, M.D. Hurtado, A.R. Brown, D.V. Boho´rquez, R.A. Liddle, H. Herzog, S. Zolotukhin, C.D. Dotson, Modulation of taste responsiveness by the satiation hormone peptide YY. FASEB J. 27, 5022–5033 (2013)

23. B. Palouzier-Paulignan, M.-C. Lacroix, P. Aime´, C. Baly, M. Caillol, P. Congar, K.A. Julliard, K. Tucker, D.A. Fadool, Olfaction under metabolic influences. Chem. Senses 37, 769–797 (2012)

24. P. Monteleone, F. Piscitelli, P. Scognamiglio, A.M. Monteleone, B. Canestrelli, V. Di Marzo, M. Maj, Hedonic eating is associated with increased peripheral levels of ghrelin and the endocannabinoid 2-arachidonoyl-glycerol in healthy humans: a pilot study. J. Clin. Endocrinol. Metab. 97, E917–E924 (2012)

25. L.M. Seoane, O. Al-Massadi, J.E. Caminos, S.A. Tovar, C. Dieguez, F.F. Casanueva, Sensory stimuli directly acting at the central nervous system regulate gastric ghrelin secretion. an ex vivo organ culture study. Endocrinology 148, 3998–4006 (2007)

26. APA, Diagnostic and Statistical Manual of Mental Disorders: DSM-5 (American Psychiatric Association, Washington, DC, 2013)

27. First, M.B. et, Spitzer, R.L., Gibbon, M., Williams, J.B.W.: Structured Clinical Interview for DSM-IV Axis I Disorders, Clinician Version (SCID-CV). (1997)

28. D.M. Garner, Eating Disorder Inventory-2 (Psychological Assessment Resources, Odessa, 1991)

29. L.R. Derogatis, SCL-90-R Symptom Checklist-90-R. Administration, Scoring and Procedures Manual (National Computer System, Minneapolis, 1994)

30. T. Van Strien, J.E. Frijters, G. Bergers, P.B. Defares, The Dutch Eating Behavior Questionnaire (DEBQ) for assessment of restrained, emotional, and external eating behavior. Int. J. Eat. Disord. 5(2), 295–315 (1986)

31. G. Kobal, T. Hummel, B. Sekinger, S. Barz, S. Roscher, S. Wolf, ‘‘Sniffin’’ Sticks’: screening of olfactory performance. Rhinology. 34, 222–226 (1996)

32. T. Hummel, B. Sekinger, S.R. Wolf, E. Pauli, G. Kobal, ‘‘Sniffin’’ sticks’. Olfactory performance assessed by the combined testing of odor identification, odor discrimination and olfactory threshold. Chem. Senses 22, 39–52 (1997)

33. A. Haehner, C. Tosch, M. Wolz, L. Klingelhoefer, M. Fauser, A. Storch, H. Reichmann, T. Hummel, Olfactory training in patients with Parkinson’s disease. PLoS ONE 8, e61680 (2013)

34. C. Mueller, S. Kallert, B. Renner, K. Stiassny, A.F.P. Temmel, T. Hummel, G. Kobal, Quantitative assessment of gustatory function in a clinical context using impregnated ‘‘taste strips’’. Rhinology. 41, 2–6 (2003)

35. R.B. Kline, Principles and practice of structural equation modeling (The Guilford Press, New York, 2010)

36. S. Trellakis, S. Tagay, C. Fischer, A. Rydleuskaya, A. Scherag, K. Bruderek, S. Schlegl, J. Greve, A.E. Canbay, S. Lang, S. Brandau, Ghrelin, leptin and adiponectin as possible predictors of the hedonic value of odors. Regul. Pept. 167, 112–117 (2011)

37. M.R. Druce, M.A. Wren, J.A. Park, J.E. Milton, M. Patterson, G. Frost, M.A. Ghatei, C. Small, S.R. Bloom, Ghrelin increases food intake in obese as well as lean subjects. Int. J. Obes. (Lond). 29, 1130–1136 (2005)

38. M. Tscho¨p, C. Weyer, P.A. Tataranni, V. Devanarayan, E. Ravussin, M.L. Heiman, Circulating ghrelin levels are decreased in human obesity. Diabetes 50, 707–709 (2001)

39. N. Thiebaud, M.C. Johnson, J.L. Butler, G.A. Bell, K.L. Ferguson, A.R. Fadool, J.C. Fadool, A.M. Gale, D.S. Gale, D.A. Fadool, Hyperlipidemic diet causes loss of olfactory sensory neurons, reduces olfactory discrimination, and disrupts odor-reversal learning. J. Neurosci. 34, 6970–6984 (2014)

40. B.E. Richardson, E.A. Vander Woude, D.A. Leopold, J.S. Thompson, Gastric bypass does not influence olfactory function in obese patients. Obes. Surg. 22, 283–286 (2012)

41. J.D. Cameron, G.S. Goldfield, E ´ . Doucet, Fasting for 24 h improves nasal chemosensory performance and food palatability in a related manner. Appetite. 58, 978–981 (2012)

Table 1 Descriptives for sample

	Anorexia (N=64)	Young controls (N=80)	Old controls (N=36)	Obese (N=59)	[1]*p*
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	.059
Use of tobacco; *%*	26.6	25.0	36.1	20.3	.339
Body Mass Index (current); *mean (SD)*	17.4 (1.4)	21.6 (2.9)	22.4 (2.6)	42.7 (6.6)	<.001
TANITA masa grasa	7.2 (3.0)	15.6 (5.6)	16.6 (5.1)	51.6 (12.8)	<.001
TANITA masa L g	39.7 (3.7)	43.7 (4.1)	43.6 (4.4)	61.9 (7.8)	<.001
TANITA tc water	28.7 (3.0)	31.5 (2.9)	31.2 (3.2)	44.4 (5.6)	<.001
EDI2-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

[1]*p* based on chi-square test for categorical descriptive and ANOVA for quantitative.

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

	Adjusted means and SE				Factor		Pair-wise (post-hoc) comparisons					
	Anorexia	Young contr.	Old contr.	Obese	Diagnosis		YC	OC	OB	OC	OB	OB
	(AN, *n*=64)	(YC, *n*=80)	(OC, *n*=36)	(OB, *n*=59)	$F_{3,217}$	[1]*p*	vs AN	vs AN	vs AN	vs YC	vs YC	vs OC
Threshold for smell (olfactory)	8.78; 0.36	6.42; 0.30	7.14; 0.44	5.99; 0.35	14.77	**<.001**	**2.36***	**1.64***	**2.79***	-0.72	0.43	**1.15***
Discrimination olfactory: correct	13.0; 0.31	12.5; 0.26	13.2; 0.38	12.5; 0.31	1.968	.120	0.49	-0.23	0.53	-0.72	0.03	0.76
Identification olfactory: correct	13.0; 0.31	13.1; 0.26	12.8; 0.38	11.8; 0.31	3.368	**.026**	-0.10	0.26	**1.20***	0.36	**1.30***	**0.94***
Threshold discrimin.-identific.	34.8; 0.67	32.0; 0.56	33.1; 0.82	30.3; 0.66	9.994	**<.001**	**2.75***	1.67	**4.52***	-1.08	1.77	**2.85***
Taste strips sweet	3.10; 0.15	3.47; 0.13	3.58; 0.18	3.25; 0.15	1.820	.241	**-0.37***	-0.48	-0.15	-0.11	0.22	0.33
Taste strips acid	2.20; 0.16	2.37; 0.14	2.50; 0.20	1.94; 0.17	2.213	.241	-0.17	-0.30	0.26	-0.13	0.43	**0.56***
Taste strips salty	2.74; 0.19	2.85; 0.17	2.73; 0.23	2.46; 0.20	0.631	.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	.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	.241	-1.02	-0.95	0.27	0.07	1.29	1.22

[1]*p-value* includes Bonferroni-Simes correction for multiple comparisons. *Bold: significant coefficient (05 level).

Table 3 Comparison of hyposmia-hypogeusia among diagnostic subtypes

	Adjusted prevalences; second line: 95% CI prev.				Logistic regression adjusted by age, depression, smoking and contraceptives						
	Anorexia	Young cont.	Old cont.	Obese	Diagn.	Contrasts: OR; *p;* second line 95% CI for OR					
	(AN, *n*=64)	(YC, *n*=80)	(OC, *n*=36)	(OB, *n*=59)	[1]*p*	YC vs AN	OC vs AN	OB vs AN	OC vs YC	OB vs YC	OB vs OC
Hyposmia	6.44%	33.0%	23.6%	54.3%	**<.001**	***5.63; .004***	3.37; *.129*	***12.7; .001***	0.60; *.414*	2.26; *.139*	***3.77; .014***
	2.45÷15.0	23.2÷43.4	11.7÷38.1	41.7÷66.3		1.75÷18.1	0.70÷16.1	3.53÷45.7	0.18÷2.05	0.77÷6.64	1.31÷10.9
Hypogeusia	18.0%	14.4%	9.33%	21.40%	.494	0.69; *.487*	0.42; *.267*	1.06; *.923*	0.61; *.506*	1.54; .512	2.51; .137
	9.88÷28.2	8.79÷24.4	4.41÷25.3	13.5÷34.1		0.24÷1.97	0.09÷1.94	0.33÷3.46	0.14÷2.60	0.43÷5.56	0.75÷8.44

*Bold: significant coefficient (05 level). Hosmer-Lemeshow: *p*=.716 (model for hyposmia) and *p*=.333 (model for hypogeusia). Total sample (*n*=239).

Table 4 Comparison of Eating Style and Hormonal factors: ANOVA adjusted by age, depression, smoking and contraceptives

	Adjusted means and SE				Factor		Pair-wise (post-hoc) comparisons					
	Anorexia	Young contr.	Old contr.	Obese	Diagnosis		YC	OC	OB	OC	OB	OB
	(AN, *n*=64)	(YC, *n*=80)	(OC, *n*=36)	(OB, *n*=59)	$F_{3,217}$	[1]*p*	vs AN	vs AN	vs AN	vs YC	vs YC	vs OC
DEBQ- total CE	21.87; 1.88	30.82; 1.55	26.32; 2.27	34.11; 1.86	10.77	<.001	**8.96***	4.45	**12.24***	-4.51	3.28	**7.79***
DEBQ- total EX	21.09; 1.19	30.98; 0.99	30.70; 1.44	30.63; 1.17	17.26	<.001	**9.89***	**9.61***	**9.54***	-0.28	-0.35	-0.07
DEBQ- total RES	30.55; 1.48	22.22; 1.23	25.72; 1.78	28.78; 1.44	7.39	<.001	**-8.33***	-4.83	-1.77	3.50	**6.56***	3.06
PYY	1.67; 0.10	1.64; 0.08	1.52; 0.10	1.70; 0.09	0.85	.933	-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	**-423.6***	140.6	**-380.7***	**-521.3***
Cholecystokinin (CCK)	1.43; 0.10	1.52; 0.08	1.52; 0.10	1.56; 0.09	0.36	.933	0.09	0.09	0.13	0.00	0.04	0.04
Orexin	2.53; 0.18	3.05; 0.15	2.80; 0.19	3.16; 0.17	3.78	.035	**0.52***	0.27	**0.63***	-0.25	0.11	0.36

[1]*p-value* includes Bonferroni-Simes correction for multiple comparisons. *Bold: significant coefficient (05 level).

Table 5 Multiple regression valuing the predictive capacity of hyposmia-hypogeusia, hormones and DBQ-CE on BMI.

Criterion: body mass index (kg/m^2)	B	SE(B)	Beta	*p*	95% CI (for B)	
First step: covariates						
Age	0.650	0.079	.535	<.001	0.495;	0.805
SCL-90-R: depression	2.489	0.820	.195	.003	0.869;	4.108
Smoking	0.497	1.600	.020	.757	-2.663;	3.656
Contraceptives	-0.632	1.622	-.026	.697	-3.835;	2.571
ΔR^2=.335; *p<.001*						
Second step: smell-taste						
Age	0.580	0.076	.478	<.001	0.430;	0.730
SCL-90-R: depression	1.861	0.804	.146	.022	0.272;	3.449
Smoking	0.479	1.515	.020	.752	-2.513;	3.471
Contraceptives	-0.315	1.538	-.013	.838	-3.352;	2.722
Hyposmia (yes vs no)	5.789	1.425	.250	<.001	2.974;	8.604
Hypogeusia (yes vs no)	3.881	1.942	.127	.047	0.046;	7.715
ΔR^2=.077; *p<.001*						
Third step: hormones-CE						
Age	0.479	0.068	.395	<.001	0.346;	0.613
SCL-90-R: depression	1.004	0.726	.079	.168	-0.429;	2.438
Smoking	0.304	1.322	.012	.818	-2.307;	2.916
Contraceptives	-0.677	1.348	-.027	.616	-3.339;	1.985
Hyposmia (yes vs no)	3.734	1.286	.161	.004	1.194;	6.274
Hypogeusia (yes vs no)	1.410	1.744	.046	.420	-2.035;	4.854
PYY	0.969	1.462	.043	.509	-1.919;	3.856
Ghrelin	-0.010	0.002	-.352	<.001	-0.014;	-0.007
Cholecystokinin (CCK)	-1.343	1.451	-.059	.356	-4.210;	1.523
Orexin	0.536	0.672	.044	.426	-0.791;	1.863
DEBQ: total CE	0.175	0.052	.190	.001	0.072;	0.278
ΔR^2=.161; *p<.001*						

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

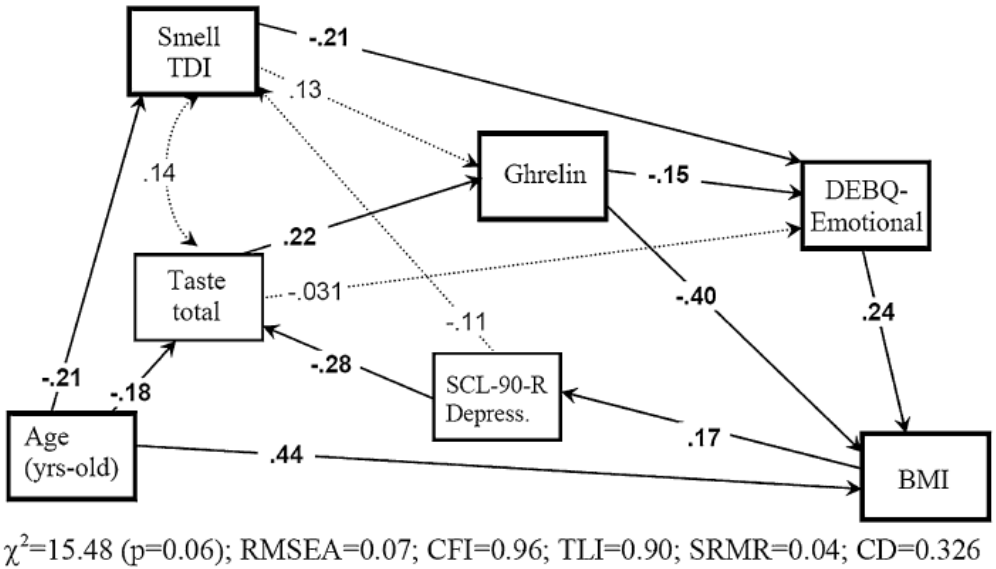

Figure 1. Pathway valuing the association between smell-taste, ghrelin, DEBQ-CE and body mass index (BMI) (controlled to age and depression score). Dash-line: non-significant association.