A tasting experiment comparing food and nutritional supplement in anorexia nervosa

A tasting experiment comparing food and nutritional supplement in anorexia nervosa

Marzola Enrica, Cavallo Fabio, Pradella Paolo, Brustolin Annalisa, Abbate-Daga Giovanni[§]

Eating Disorders Center for Treatment and Research, Department of Neuroscience, University of Turin, Via Cherasco 11, 10126, Turin, Italy

[§] Corresponding author:

Prof. Giovanni Abbate-Daga

Director of the Eating Disorders Center

Department of Neuroscience

University of Turin,

Via Cherasco 11, 10126, Turin, Italy

Tel and fax: +39 011 6335749

Email: giovanni.abbatedaga@unito.it

Abstract

Anorexia nervosa (AN) is a severe psychiatric disorder leading to life-threatening emaciation. Weight restoration is crucial in treatment but few data are available on how to achieve it. Nutritional supplements are needed in treatment but patients' preferences about natural versus medical foods and their gustatory/hedonic perception are unclear. We aimed to measure disgust and reward-based eating in AN and to assess psychological, interoceptive awareness-related, behavioral, and hedonic aspects comparing natural versus medical food. Thirty-three inpatients with AN and 39 healthy controls (HCs) were recruited and received 50 ml of either apricot juice or nutritional liquid supplement with apricot flavor on two consecutive days. Disgust, reward-based eating, and eating psychopathology were evaluated. Visual Analogue Scales measuring anxiety, hunger, confusion about internal states, need for over-exercise, restraint, and satiety were completed before and after the experiment. Disgust and hedonic responses were measured after the experiment. Patients with AN reported preserved disgust sensitivity and higher reward-based eating drive. When compared to HCs, inpatients with AN reported higher scores on anxiety, hunger, confusion about internal states, urge to over-exercise, urge to eating restraint, and satiety before and after the tasting experiment. The supplement slightly increased patients' anxiety with HCs reporting the same trend. Still, patients reported more food-related disgust after the supplement but their overall hedonic evaluation was similar for both conditions. Also, anxiety, confusion about internal states, and urge to over-exercise and restraint did not significantly increase after consuming either food. Therefore, if we take into account patients' level of heightened satiety and suppressed hunger, supplements could be helpful for patients with severe AN since greater energy intakes could be provided with only small volumes of food and little changes of eating concerns.

Keywords: eating disorders, medical foods, weight restoration, anxiety, interoceptive awareness, hospitalization

1. Introduction

Anorexia nervosa (AN) is a severe psychiatric disorder characterized by persistent restriction of food intake at times alternated by breakdowns of inhibition (i.e., binges) and dangerous purging behaviors, fear of being "fat" despite severe emaciation, obsessive thoughts about food and weight, and disturbance in the way in which one's body weight or shape is experienced. Currently, treatment outcomes are highly unsatisfactory with psychiatric comorbidity and mortality being very high (Smink, Van Hoeken, & Hoek, 2012).

Although a key aspect of the treatment of AN is weight restoration (American Psychiatric Association [APA], 2010; National Institute for Health and Care Excellence [NICE], 2017), food aversion represents a hallmark of this disorder and one of the main obstacles to treatment (Fassino & Abbate-Daga, 2013). Gustation is crucial in guiding one's own food choices, including food approach, selection, preference, and avoidance (Van Dongen, Van Den Berg, Vink, Kok, & De Graaf, 2012). Quantities and qualities/textures of what we eat are guided by sensory and metabolic processes. Several studies deepened the tasting function in AN (Kinnaird, Stewart, & Tchanturia, 2018), with the overarching aim to expand knowledge on potential etiology and maintenance factors, including taste perception, in turn improving the available treatment options.

The available body of evidence on taste sensitivity in AN is somehow mixed and only partially connected to clinical practice. With more detail, the literature on taste in the field of eating disorders focused mainly on gustatory sensitivity and hedonic response to taste stimuli. Earlier papers reported a preserved gustatory sensitivity in AN (Drewnowski, 1989) while more updated studies did not confirm this finding, as reported in a recent review proposing an altered taste sensitivity in AN that may improve after recovery (Kinnaird, Stewart, & Tchanturia, 2018). Besides, patients with AN showed decreased taste reactivity (Szalay et al., 2010) with behavioral therapy potentially improving taste responsiveness (Nozoe et al., 1996). Concerning the hedonic perception of taste, literature reports patients affected by bulimia nervosa having a greater preference for sweet foods than those with AN, characterized by fat aversion instead (Chao, Roy,

Franks, & Joseph, 2020). Also, an earlier study demonstrated that patients with AN tend to dislike foods rich in fats but their perception of the sweet taste was preserved (Simon, Bellisle, Monneuse, Samuel-Lajeunesse, & Drewnowski, 1993). Interestingly, an investigation on the hedonic aspects of gustation in AN reported that the hedonic response to sucrose was lower if patients were asked to swallow versus spit the sweet solution (Eiber, Berlin, De Brettes, Foulon, & Guelfi, 2002).

Tasting is linked to reward processes in the brain; the reward network is known to impact on the development and maintenance of AN (Berner et al., 2019); in this regard, patients' taste experience represents the very first step of such a crucial reward pathway. The taste is fundamental in modulating eating behaviors: its alterations can influence directly food drive and food avoidance alike (Ventura & Worobey, 2013). Neuroimaging studies, using taste stimuli, reported altered or reduced activation of the insula (i.e., primary gustatory cortex), in patients with AN, compared to HCs (Frank, Shott, Keffler, & Cornier, 2016; Wagner et al., 2008). Relatedly, women recovered from AN reported different insula activations is consuming sucrose versus sucralose (i.e., sucrose-like sweet taste but no calories) solutions (Oberndorfer et al., 2013) and very recent data highlighted a neural insensitivity of patients with AN to the hunger stimulus (Kaye et al., 2020).

Notwithstanding the aforementioned literature, it turns out that only scant data are available on taste perception as applied to “real-world” contexts. For example, in every-day practice, mostly when working with patients with severe AN, the use of nutritional supplements is not only common but also much needed (Marzola, Nasser, Hashim, Shih, & Kaye, 2013). The clinical rationale for using medical foods as supplements is at least three-fold: a) they can provide vitamin and mineral needs; b) gastric emptying of solid meals tends to be delayed in AN while liquid meals are more tolerable; c) energy-dense foods are helpful to avoid abdominal bloating when patients' emaciation requires intense daily energy amounts. Despite several clinical benefits, clinicians know well that some AN sufferers are really frightened by nutritional supplements because of their energy density. In contrast, other patients prefer medical foods to natural foods because the former are seen as medications bypassing the use of real foods. Whatever the clinical presentation, studies providing

quantitative measures on patients' preferences regarding natural versus medical foods and their gustatory and hedonic perception are currently lacking.

To help bridging the aforementioned gaps in literature we designed a standardized tasting experiment asking patients with AN and healthy controls (HCs) to taste on two consecutive days 50 ml of either apricot juice (28 kcal) or nutritional liquid supplement (75 kcal) with apricot flavor and to complete a battery of assessments before and after the tasting experiment. Keeping the volume constant while modulating energy intake, we attempted to disentangle what could be related to patients' satiety versus their eating-related cognitive aspects. Therefore, with the overarching goal to inform treatments on the use of medical foods in the treatment of AN we aimed: a) to measure disgust sensitivity and reward-based eating in patients with AN and HCs; b) to assess differences on a variety of psychological (i.e., anxiety) and interoceptive awareness-related (i.e., hunger, satiety, confusion about internal states), behavioral (i.e., urge to over-exercise, urge to eating restraint) and hedonic (food-related hedonic evaluation and disgust) between groups (i.e., AN versus HCs) across conditions (i.e., juice day versus supplement day) on two different time points (i.e., before and after the tasting experiment).

Our a priori hypothesis was to find differences in disgust perception between patients with AN and HCs with the latter group showing more reward-driven eating. Still, we expected to find patients with AN as showing differences when compared to HCs, mostly concerning the comparison between juice versus supplement condition.

2. Methods

2.1 Participants

Inpatients consecutively and voluntarily admitted to the Psychiatry ward of the Eating Disorders Center of the University of Turin, at the "Città della Salute e della Scienza" hospital of Turin, Italy, were initially asked to participate in this study between February and November 2019.

Inclusion criteria for patients were the following: a) diagnosis of AN as assessed with the Structured Clinical Interview for DSM-5 (First, Williams, Karg, & Spitzer, 2016) by an experienced psychiatrist upon admission; b) female gender; c) no substance dependence; c) no psychotic – spectrum disorders; d) no organic comorbidities (e.g., diabetes). Out of the 45 patients interviewed, 6 did not meet the inclusion criteria, 5 refused participation and 1 failed to complete the assessment battery. Therefore, 33 inpatients were finally enrolled.

Healthy controls (HCs) were recruited at the same Institution through flyers and word of mouth and a total of 39 HCs (i.e., medical students, psychology students, residents, individuals who were interested in giving their moral contribution to the research) were finally enrolled. Inclusion criteria for HCs were: a) being free of psychotropic medications; b) not meeting criteria for a current or lifetime diagnosis of EDs or other psychiatric disorders, as assessed by an experienced psychiatrist.

Participants were all Caucasian and a trained nurse measured everyone's height and weight to calculate their body mass index (BMI).

The Ethical Committee of the Department of Neuroscience of the University of Turin, Italy, approved this study and all participants provided their written informed consent.

2.2 Procedure

To run the tasting experiment, all participants were assigned to receive 50 ml of either apricot juice (28 kcal) or nutritional liquid supplement (75 kcal) with apricot flavor on two consecutive days. Participants were unaware of the energy value of the foods. No previous data were available to set a standardized quantity of juice/supplement; so the volume was set at 50 ml in order to ensure research feasibility (also avoiding the bias related to patients' potential feeling of "fullness"). Also, the volume was kept constant with a different energy intake (almost three times as

much for the medical food), to clarify what could be related to patients' satiety versus their cognitive aspects. The apricot taste was standardized to avoid individual preferences (e.g., apricot versus strawberry). The order of administration (i.e., juice on day 1 or day 2) was randomized in order to avoid bias since the second administration could be influenced by the one received on the day before. All patients were amenorrheic; HCs were not tested during the week preceding their menses to avoid hormonal-related food craving to be a confounder. Participants were asked to assess on a 10-cm Visual Analogue Scale anxiety, hunger, confusion about internal states, need for physical activity, restraint, and satiety before and after the experiment on both days. Participants' disgust and hedonic responses were also measured after the experiment on both days. Participants were tested at 11 a.m. after a fasting period of 2.5 hours following a standardized morning breakfast of 250 kcal at 8.30 am. Inpatients were assessed during the first week of their hospital stay. If enteral or parenteral nutrition was required for patients, it was administered during the remaining hours of the day (i.e., afternoon). Also, all inpatients were informed that any eventual changes in their total daily energy intake (as decided with an individualized behavioral contract) would have been adjusted for the consumption of either juice or liquid supplement, to make it clear that study participation would not bring about any energy increases.

2.3 Measures

At study entry, all participants provided socio-demographical and clinical information and were asked to complete the following assessments:

- Disgust scale (Haidt, Mccauley, & Rozin, 1993): is a 32 items questionnaire that measures sensitivity and includes 2 true-false and 2 disgust-rating items for each of seven domains of disgust elicitors (food, animals, body products, sex, body envelope

violations, death, and hygiene) and for a domain of magical thinking (via similarity and contagion) that cuts across the seven domains of elicitors.

- Reward-based eating scale (Epel et al., 2014): some individuals report factors that drive overeating, including lack of control, lack of satiation, and preoccupation with food, which may stem from reward-related neural circuitry. This 9-item scale captures reward-based eating drive as a single factor, with high internal consistency and invariance across demographic factors.
- Eating disorder examination (EDE-Q; Luce & Crowther, 1999): a 41 items semi-structured interview conducted by a clinician in the assessment of an eating disorder. EDE-Q provides four subscales (restraint, eating concern, shape concern and weight concern) and a global score.
- Hedonic scale (Peryam & Pilgrim, 1957): the hedonic scale indicates general levels of preference of a stimuli (actual samples or food names) with 9 categories ranging from "dislike extremely" to "like extremely."

Before and after the experiment all participants completed a battery of Visual Analogue Scales (VAS) measuring, on a 10-cm line, the following: a) anxiety, b) hunger; c) confusion about internal states; d) urge to over-exercise; e) urge to eating restraint; f) satiety.

After the tasting experiment, all participants completed a VAS measuring food-related disgust and the hedonic scale (Peryam & Pilgrim, 1957).

2.4 Statistical analysis

The SPSS 25.0 statistical software package (IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp) was used for all analyses.

Student's t-test for independent samples was used to evaluate the differences between AN and HC groups on all the baseline assessment batteries.

A mixed-model repeated-measures ANOVA was performed to investigate any differences occurred over time (i.e., before and after the tasting experiment), between groups (i.e., AN versus HCs), and across conditions (i.e., juice day versus supplement day). The effect size was measured with the Eta Squared (η^2). According to Cohen's work (Pierce, Block, & Aguinis, 2004), the effect size can be assessed as small η^2=0.01-0.06; moderate η^2=0.06-0.14; or large η^2>0.14.

3. Results

3.1 Sociodemographic and clinical characteristics of the sample

A total of 33 female inpatients with AN were enrolled: 21 were diagnosed with the restricting type of AN (R-AN) and 12 by the binge-purging type of AN (BP-AN). Thirty-nine female HCs were recruited as well so the total sample was 72.

Sociodemographic characteristics are shown in Table 1. Concerning clinical variables, those with AN and HCs differed with respect to BMI but had similar age (see Table 1). Patients' duration of illness was 7.8±8.6 years [range: 0.25 – 30 years]; four patients (12%) were receiving parenteral and 11 (33%) enteral nutrition. Patients and HCs differed on all subscales of eating psychopathology as measured by the EDE-Q (Table 1).

----------PLEASE INSERT TABLE 1 AROUND HERE----------

3.2 Disgust sensitivity and reward-based eating

As shown in Table 1, patients and HCs did not differ on the disgust scale but significantly differed on the reward-based eating scale (see Table 1).

3.3 Correlations between disgust, reward-based eating and eating psychopathology

No correlations were found between disgust and eating psychopathology in either group (see Table 2). Concerning reward-based eating, patients with AN reported significant correlations with the EDE-Q total score and all subscales but restraint (Table 2). In contrast, HCs did not show any significant correlations with either scale (Table 2); therefore, only patients with AN showed higher reward-based eating as correlated with more severe eating psychopathology.

----------PLEASE INSERT TABLE 2 AROUND HERE----------

3.4 The tasting experiment

3.4.1. Group differences in the taste experiment

As shown in Table 3, patients with AN and HCs displayed between-subjects significant differences with large effect sizes on all measures considered (Figure 1) with the exception of the hedonic scale that did not reach statistical significance between groups (Figure 2). Thus, these findings indicate a very different subjective evaluation for all food-related aspects; in contrast, hedonic evaluation was not impaired in AN.

3.4.2. Time-related changes before and after the tasting experiment

Significant changes before and after the tasting experiment were reported only for hunger and satiety; therefore, the scores of all other considered variables (i.e., anxiety, confusion, need for physical activity, and restraint) were similar over time.

3.4.3. Condition-related differences in the tasting experiment

Some significant differences comparing conditions (i.e., juice versus supplement) emerged in anxiety, disgust, and hedonic response. In fact, participants were more anxious when consuming

the supplement as compared to the juice and they were less disgusted by the juice than by the supplement. The hedonic response showed also a significant group-by-condition interaction (see below).

3.4.4. Interactions between condition and group in the tasting experiment

The hedonic scale reported not only a significant effect of condition, but also a significant interaction between condition (i.e., juice versus supplement) and group (i.e., AN versus HCs). That is, being affected by AN significantly impacted on the hedonic evaluation of the food: in fact, patients with AN deemed juice and supplement as equally pleasant while HCs reported higher hedonic value for the juice.

3.4.4. Interactions between time and group in the tasting experiment

Significant interactions between time (i.e., differences in scores reported before and after the tasting experiment) and group (i.e., AN versus HCs) were seen for the need for physical activity; in fact, only patients with AN reported hightened drive to over-exercise after the experiment (in both conditions) while HCs' need for physical activity remained the same (or even lowered) after receiving juice or medical supplement.

----------PLEASE INSERT TABLE 3 AROUND HERE----------

4. Discussion

Our investigation of taste perception in AN in the real-world setting of the hospital stay yielded several main findings: first, we found not only a maintained ability to perceive disgust in AN but also more reward-based eating (directly correlated with eating psychopathology) in AN than in HCs. Second, our study clarified that inpatients with AN and HCs report profound (i.e., with large effect sizes) differences on all the measured taste-related aspects of eating. In particular,

patients with AN reported markedly greater anxiety, hunger, confusion about internal states, need for physical activity, urge to eating restraint, and satiety than HCs. Thirdly, food-related hedonic response were intact in AN; nevertheless, it is of note that patients reported equal hedonic values for real versus medical foods, while HCs showed a more fine-grained reponse depending on the food stimulus considered (that is, HCs preferred the juice). Finally, in AN, the supplement elicited more anxiety and food-related disgust than the juice with HCs showing the same trend.

In contrast with our a priori hypothesis, patients with AN were shown to have maintained disgust sensitivity. Research on this topic is currently growing in the field of eating disorders (Harris et al., 2019; Menzel, Reilly, Luo, & Kaye, 2019) but, to date, the findings on disgust in AN are overall mixed (Troop, Murphy, Bramon, & Treasure, 2000;Aharoni & Hertz, 2012; Davey, Buckland, Tantow, & Dallos, 1998). Also, the disgust scale did not show significant correlations with eating psychopathology for either patients or HCs. Therefore, our findings suggest that disgust sensitivity could be not only preserved in AN but also unrelated to the core features of AN psychopathology. Given the debate on these aspects (Harris et al., 2019; Menzel et al., 2019), future studies are needed to clarify this discrepancy; nevertheless, differences in assessment tools could account for this difference as well as the sample composition, namely severe hospitalized patients.

Strikingly, those with AN reported higher reward-based drive to eat than HCs. It is difficult to compare this result with the existing literature since this scale has not been used so far in the field of eating disorders. Nevertheless, differences between subgroups of AN could impact on this observation with those diagnosed with the binge-purging subtype being particularly impulsive over food (Pryor, Wiederman, & McGilley, 1996). Also, some questions (e.g., “When I start eating, I just can’t seem to stop”; “Food is always on my mind”) could be somehow misleading since more focused on preoccupation for food instead of reward. Therefore, patients with AN could have scored higher because they are typically frightened by the possibility of losing control over food. In keeping with this hypothesis, those between patients' reward-based eating scale and eating

psychopathology were the only significant correlations. Still, it could not be ruled out that psychopathology severity could be associated with drive for food that patients could mislabel as reward-based eating.

According to the a priori hypothesis, HCs and patients with AN reported significantly different scores on all psychological (i.e., anxiety), interoceptive awareness-related (i.e., hunger, satiety, confusion about internal states), behavioral (i.e., urge to over-exercise, urge to eating restraint) and food-related disgust assessments, with large effect sizes. Although expected, based on clinical experience and previous data (Kaye et al., 2020; Marzola et al., 2016), this difference has been measured in a real-world setting entailing for participants the consumption of real food. Things change for patients when they know that they will have to consume the food they are presented with (Milos et al., 2013). Therefore, these findings could contribute to expand therapists' knowledge of how difficult for patients with AN is to approach both natural and medical food.

Focusing on the differences found in the AN group between the juice and supplement conditions with the overarching goal of potentially informing treatments, it is of note that the medical food resulted to be more anxiogenic for patients when compared to the juice; however, anxiety, confusion about internal states, and urge to both over-exercise and restrict food intake did not significantly increase after consuming either food. Similarily, both juice and supplement significantly increased satiety and lowered hunger, a painful stimulus for AN sufferers (Sunday & Halmi, 1996; Westmoreland, Krantz, & Mehler, 2016). Still, patients reported more food-related disgust after the supplement but their hedonic evaluation was the same for both conditions. Therefore, if we take into account that patients' level of satiety/hunger were markedly different than those of HCs, medical foods could be helpful in treatment since greater energy intakes could be provided with small volumes of food. Taken together, these findings can be of clinical relevance: on one hand, the supplement entails heightened levels of anxiety but on the other hand, it is also true that the fruit juice generates marked anxiety anyway.

It is of note that the aforementioned results have not been biased by the issue of food portion since the volume was kept constant so we found patients with AN as being more anxious when evaluating the nutritional supplement, independently of the portion size. Previous lines of research on patients' portion size assessment in AN reported that visual size determined patients' anxiety more than the energy density of the food (Kissileff et al., 2016). Our study garners innovative data showing that, if the portion size is kept constant, calories do not extremely impact on patients' anxiety which does not increase after consuming either natural or medical foods. However, this comparison could be hampered by the different study design: our sample was composed of severe inpatients who knew that the presented food had to be eaten, and not only measured, during the experiment. This could promote the activation of top-down cognitive aspects aimed at handling the long-term consequences of eating behavior (Kaye, Fudge, & Paulus, 2009).

Patients with AN and HCs scored differently on the food-related disgust assessment and a significant main effect of condition emerged as well. That is, patients with AN were more disgusted after tasting the apricot-flavor supplement than the apricot juice. Therefore, this finding puts disgust in AN in a broader perspective: in fact, on one hand disgust perception is overall maintained in AN, but on the other hand, when focusing on food-related aspects, patients with AN perceive disgust much more markedly than HCs.

Differently from our a priori hypothesis, patients with AN reported food-related hedonic values comparable to those of HCs so this was the only assessment that did not differ between groups. Assuming that the hedonic scale includes the assessment of the cognitive component of taste, it is noteworthy that patients with AN, although potentially more anxious given the supplement condition, found equally rewarding the juice and the supplement. In the light of the current debate on reward in AN (Kaye, Wierenga, Bailer, Simmons, & Bischoff-Grethe, 2013; Kaye et al., 2020) this is of clinical interest since these findings open up the possibility that also more energy-dense food could not impact on patients' hedonic response. Once more, patients' cognitive

"top-down" brain circuits of control could be more activated than those of the "bottom-up" brain networks, involved in the hedonic response and pleasure of a certain stimulus (Kaye et al., 2013). However, it could be argued that, during their evaluations, patients could find other elements than the taste itself as rewarding, like perceiving supplements as medications rather than real food.

In spite of some strengths like the real-world setting, the control of hunger (Tapper, 2005), the measurement of hunger and satiety before the experiment, and the quantitative measurement of refeeding aspects with severe patients, this study suffers from some limitations as well: inpatients in a very acute phase of AN were recruited, no longitudinal data are available, and data generalizability could be hampered by the kind (i.e., brand) of medical food used. Finally, participants' were not asked about their overall preference between real versus medical food.

In closing, our data show that the use of medical foods (i.e., nutritional supplements) is not contraindicated in the treatment of severe AN. In fact, patients tolerated equally well, from a hedonic perspective, both foods although they reported the supplement as slightly more anxiogenic and disgusting than the juice. Notwithstanding the between-group difference, HCs reported the same trend for anxiety and disgust, albeit with a different magnitude. Also, neither juice nor the supplement significantly increased over time patients' scores of anxiety, confusion about internal states, and urge to restraint. Finally, when compared to HCs, patients' reported scarce hunger coupled with heightened satiety with very large effect size. Taken together, these findings suggest that the supplement could be a valid treatment option, useful to help patients consume an intense energy intake without entailing great volumes of food. Furthermore, a relevant energy increase (i.e., three times greater than the juice) increased anxiety only a little. That said, it is of note that anxiety, food-related disgust, heightened satiety, and tendency to physical over-exercise after meals are hallmarks of severe AN so all trained clinicians already know that these core components of the disorder have to be addressed anyway in treatment, independently of the refeeding strategy selected.

Conflict of interest

The authors have no conflicts of interest to declare.

Author contributions

GAD and EM designed the study; EM and PP conducted the assessments; EM and FC drafted the manuscript and ran the analyses; GAD supervised the analyses; AB and GAD critically revised the manuscript.

Funding sources

This is unfunded research.

Acknowledgments

None.

References

Aharoni, R., & Hertz, M. M. (2012). Disgust sensitivity and anorexia nervosa. *European Eating Disorders Review*, *20*(2), 106–110. https://doi.org/10.1002/erv.1124

American Psychiatric Association [APA]. (2010). *Practice Guideline For The Treatment of Patients With Eating Disorders Third Edition*. Retrieved from https://www.psychiatry.org/psychiatrists/practice/clinical-practice-guidelines

Berner, L. A., Brown, T. A., Lavender, J. M., Lopez, E., Wierenga, C. E., & Kaye, W. H. (2019, November 1). Neuroendocrinology of reward in anorexia nervosa and bulimia nervosa:

Beyond leptin and ghrelin. *Molecular and Cellular Endocrinology*, Vol. 497. https://doi.org/10.1016/j.mce.2018.10.018

Cascino, G., Castellini, G., Stanghellini, G., Ricca, V., Cassioli, E., Ruzzi, V., … Monteleone, A. M. (2019). The role of the embodiment disturbance in the anorexia nervosa psychopathology: A network analysis study. *Brain Sciences*, *9*(10). https://doi.org/10.3390/brainsci9100276

Chao, A. M., Roy, A., Franks, A. T., & Joseph, P. V. (2020). A Systematic Review of Taste Differences Among People With Eating Disorders. *Biological Research for Nursing*, *22*(1), 82–91. https://doi.org/10.1177/1099800419872824

Davey, G. C. L., Buckland, G., Tantow, B., & Dallos, R. (1998). Disgust and eating disorders. *European Eating Disorders Review*, *6*(3), 201–211. https://doi.org/10.1002/(SICI)1099-0968(199809)6:3<201::AID-ERV224>3.0.CO;2-E

Drewnowski, A. (1989). Taste Responsiveness in Eating Disorders. *Annals of the New York Academy of Sciences*, *575*(1), 399–409. https://doi.org/10.1111/j.1749-6632.1989.tb53260.x

Eiber, R., Berlin, I., De Brettes, B., Foulon, C., & Guelfi, J. D. (2002). Hedonic response to sucrose solutions and the fear of weight gain in patients with eating disorders. *Psychiatry Research*, *113*(1–2), 173–180. https://doi.org/10.1016/S0165-1781(02)00232-9

Epel, E. S., Tomiyama, A. J., Mason, A. E., Laraia, B. A., Hartman, W., Ready, K., … Kessler, D. (2014). The Reward-Based Eating Drive Scale: A Self-Report Index of Reward-Based Eating. *PLoS ONE*, *9*(6), e101350. https://doi.org/10.1371/journal.pone.0101350

Fassino, S., & Abbate-Daga, G. (2013, November 7). Resistance to treatment in eating disorders: A critical challenge. *BMC Psychiatry*, Vol. 13. https://doi.org/10.1186/1471-244X-13-282

Fassino, S., Pierò, A., Gramaglia, C., & Abbate-Daga, G. (2004). Clinical, psychopathological and personality correlates of interoceptive awareness in anorexia nervosa, bulimia nervosa and

obesity. *Psychopathology*, *37*(4), 168–174. https://doi.org/10.1159/000079420

First, M., Williams, J., Karg, R., & Spitzer, R. (2016). *Structured Clinical Interview for DSM-5 Disorders, Clinician Version (SCID-5-CV)*. Arlington, VA: American Psychiatric Association.

Frank, G. K. W., Shott, M. E., Keffler, C., & Cornier, M. A. (2016). Extremes of eating are associated with reduced neural taste discrimination. *International Journal of Eating Disorders*, *49*(6), 603–612. https://doi.org/10.1002/eat.22538

Haidt, J., Mccauley, C., & Rozin, P. (1993). *Individual Differences in Sensitivity to Disgust: A scale sampling seven domains of disgust elicitors*.

Harris, A. A., Romer, A. L., Hanna, E. K., Keeling, L. A., LaBar, K. S., Sinnott-Armstrong, W., … Zucker, N. L. (2019). The central role of disgust in disorders of food avoidance. *International Journal of Eating Disorders*, *52*(5), 543–553. https://doi.org/10.1002/eat.23047

Karlsson, G. P., Clinton, D., & Nevonen, L. (2013). Prediction of weight increase in anorexia nervosa. *Nordic Journal of Psychiatry*, *67*(6), 424–432. https://doi.org/10.3109/08039488.2012.754051

Kaye, W. H., Fudge, J. L., & Paulus, M. (2009, August). New insights into symptoms and neurocircuit function of anorexia nervosa. *Nature Reviews Neuroscience*, Vol. 10, pp. 573–584. https://doi.org/10.1038/nrn2682

Kaye, W. H., Wierenga, C. E., Bailer, U. F., Simmons, A. N., & Bischoff-Grethe, A. (2013). Nothing tastes as good as skinny feels: the neurobiology of anorexia nervosa. *Trends in Neurosciences*, *36*(2), 110–120. https://doi.org/10.1016/j.tins.2013.01.003

Kaye, W. H., Wierenga, C. E., Bischoff-Grethe, A., Berner, L. A., Ely, A. V., Bailer, U. F., … Fudge, J. L. (2020). Neural Insensitivity to the Effects of Hunger in Women Remitted From Anorexia Nervosa. *American Journal of Psychiatry*, appi.ajp.2019.1.

https://doi.org/10.1176/appi.ajp.2019.19030261

Kinnaird, E., Stewart, C., & Tchanturia, K. (2018, August 1). Taste sensitivity in anorexia nervosa: A systematic review. *International Journal of Eating Disorders*, Vol. 51, pp. 771–784. https://doi.org/10.1002/eat.22886

Kissileff, H. R., Brunstrom, J. M., Tesser, R., Bellace, D., Berthod, S., Thornton, J. C., & Halmi, K. (2016). Computerized measurement of anticipated anxiety from eating increasing portions of food in adolescents with and without anorexia nervosa: Pilot studies. *Appetite*, *97*, 160–168. https://doi.org/10.1016/j.appet.2015.11.026

Luce, K. H., & Crowther, J. H. (1999). The reliability of the eating disorder examination—Self-report questionnaire version (EDE-Q). *International Journal of Eating Disorders*, *25*(3), 349–351. https://doi.org/10.1002/(SICI)1098-108X(199904)25:3<349::AID-EAT15>3.0.CO;2-M

Marzola, E., Nasser, J. A., Hashim, S. A., Shih, P. an B., & Kaye, W. H. (2013, November 7). Nutritional rehabilitation in anorexia nervosa: Review of the literature and implications for treatment. *BMC Psychiatry*, Vol. 13. https://doi.org/10.1186/1471-244X-13-290

Marzola, E., Panepinto, C., Delsedime, N., Amianto, F., Fassino, S., & Abbate-Daga, G. (2016). A factor analysis of the meanings of anorexia nervosa: Intrapsychic, relational, and avoidant dimensions and their clinical correlates. *BMC Psychiatry*, *16*(1). https://doi.org/10.1186/s12888-016-0894-6

Menzel, J. E., Reilly, E. E., Luo, T. J., & Kaye, W. H. (2019). Conceptualizing the role of disgust in avoidant/restrictive food intake disorder: Implications for the etiology and treatment of selective eating. *International Journal of Eating Disorders*, *52*(4), 462–465. https://doi.org/10.1002/eat.23006

Milos, G., Kuenzli, C., Soelch, C. M., Schumacher, S., Moergeli, H., & Mueller-Pfeiffer, C. (2013).

How much should I eat? Estimation of meal portions in anorexia nervosa. *Appetite*, *63*, 42–47. https://doi.org/10.1016/j.appet.2012.12.016

National Institute for Health and Care Excellence [NICE]. (2017). Eating disorders: recognition and treatment. *NICE Guideline [NG69]*. Retrieved from https://www.nice.org.uk/guidance/ng69

Nozoe, S. I., Masuda, A., Naruo, T., Soejima, Y., Nagai, N., & Tanaka, H. (1996). Changes in taste responsiveness in patients with anorexia nervosa during behavior therapy. *Physiology and Behavior*, *59*(3), 549–553. https://doi.org/10.1016/0031-9384(95)02105-1

Oberndorfer, T. A., Frank, G. K. W., Simmons, A. N., Wagner, A., McCurdy, D., Fudge, J. L., … Kaye, W. H. (2013). Altered insula response to sweet taste processing after recovery from anorexia and bulimia nervosa. *American Journal of Psychiatry*, *170*(10), 1143–1151. https://doi.org/10.1176/appi.ajp.2013.11111745

Peryam, D. R., & Pilgrim, F. J. (1957). Hedonic scale method of measuring food preferences. *Food Technology*, *11*(Suppl.), 9–14.

Pierce, C. A., Block, R. A., & Aguinis, H. (2004). Cautionary Note on Reporting Eta-Squared Values from Multifactor ANOVA Designs. *Educational and Psychological Measurement*, *64*(6), 916–924. https://doi.org/10.1177/0013164404264848

Pryor, T., Wiederman, M. W., & McGilley, B. (1996). Clinical correlates of anorexia nervosa subtypes. *The International Journal of Eating Disorders*, *19*(4), 371–379. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/9156690

Simon, Y., Bellisle, F., Monneuse, M. O., Samuel-Lajeunesse, B., & Drewnowski, A. (1993). Taste responsiveness in anorexia nervosa. *British Journal of Psychiatry*, *162*(FEB.), 244–246. https://doi.org/10.1192/bjp.162.2.244

Smink, F. R. E., Van Hoeken, D., & Hoek, H. W. (2012). Epidemiology of eating disorders:

Incidence, prevalence and mortality rates. *Current Psychiatry Reports*, *14*(4), 406–414. https://doi.org/10.1007/s11920-012-0282-y

Sunday, S. R., & Halmi, K. A. (1996). Micro- and macroanalyses of patterns within a meal in anorexia and bulimia nervosa. *Appetite*, *26*(1), 21–36. https://doi.org/10.1006/appe.1996.0002

Szalay, C., Ábrahám, I., Papp, S., Takács, G., Lukáts, B., Gáti, Á., & Karádi, Z. (2010). Taste reactivity deficit in anorexia nervosa. *Psychiatry and Clinical Neurosciences*, *64*(4), 403–407. https://doi.org/10.1111/j.1440-1819.2010.02106.x

Tapper, K. (2005, October). Motivating operations in appetite research. *Appetite*, Vol. 45, pp. 95–107. https://doi.org/10.1016/j.appet.2005.05.002

Troop, N. A., Murphy, F., Bramon, E., & Treasure, J. L. (2000). Disgust sensitivity in eating disorders: A preliminary investigation. *International Journal of Eating Disorders*, *27*(4), 446–451. https://doi.org/10.1002/(SICI)1098-108X(200005)27:4<446::AID-EAT9>3.0.CO;2-W

Van Dongen, M. V., Van Den Berg, M. C., Vink, N., Kok, F. J., & De Graaf, C. (2012). Taste-nutrient relationships in commonly consumed foods. *British Journal of Nutrition*, *108*(1), 140–147. https://doi.org/10.1017/S0007114511005277

Ventura, A. K., & Worobey, J. (2013, May 6). Early influences on the development of food preferences. *Current Biology*, Vol. 23. https://doi.org/10.1016/j.cub.2013.02.037

Wagner, A., Aizenstein, H., Mazurkewicz, L., Fudge, J., Frank, G. K., Putnam, K., … Kaye, W. H. (2008). Altered insula response to taste stimuli in individuals recovered from restricting-type anorexia nervosa. *Neuropsychopharmacology*, *33*(3), 513–523. https://doi.org/10.1038/sj.npp.1301443

Westmoreland, P., Krantz, M. J., & Mehler, P. S. (2016, January 1). Medical Complications of Anorexia Nervosa and Bulimia. *American Journal of Medicine*, Vol. 129, pp. 30–37.

https://doi.org/10.1016/j.amjmed.2015.06.031

Figure 1. Pre- and post-experiment differences between patients with anorexia nervosa and healthy controls in anxiety, hunger, confusion about internal states, restraint, need for physical activity, and satiety.

Figure 1a. Anxiety was significantly different between groups and a significant effect of condition (i.e., juice versus supplement) emerged. Range of mean scores: 4.3 – 29.5.

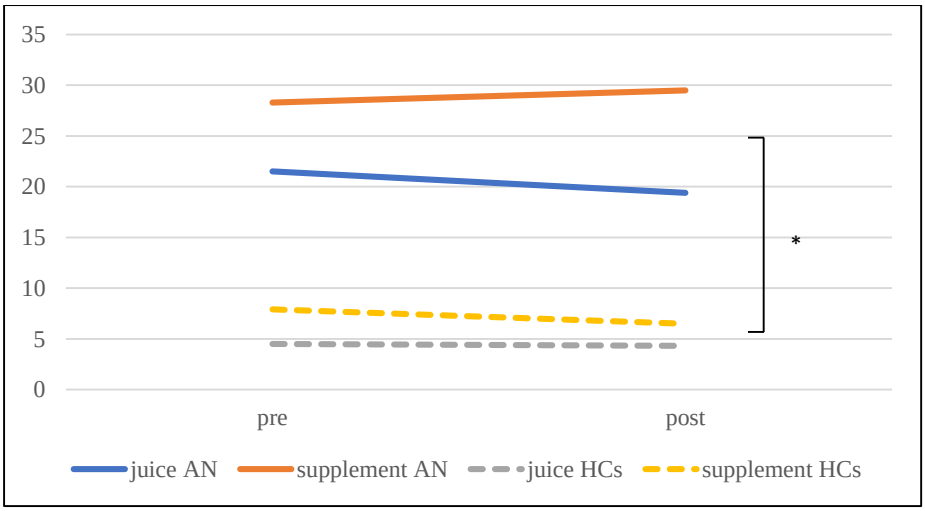

Figure 1b. Hunger was significantly different between groups and a significant effect of time (i.e., before and after the experiment) emerged. Range of mean scores: 9.5 – 31.9.

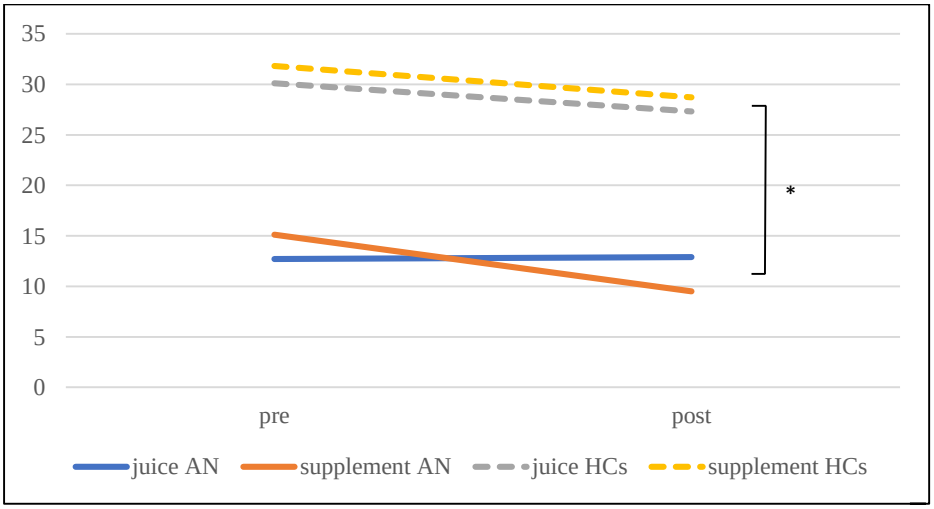

Figure 1c. Confusion about internal states was significantly different between groups. Range of mean scores: 1.8 – 22.4.

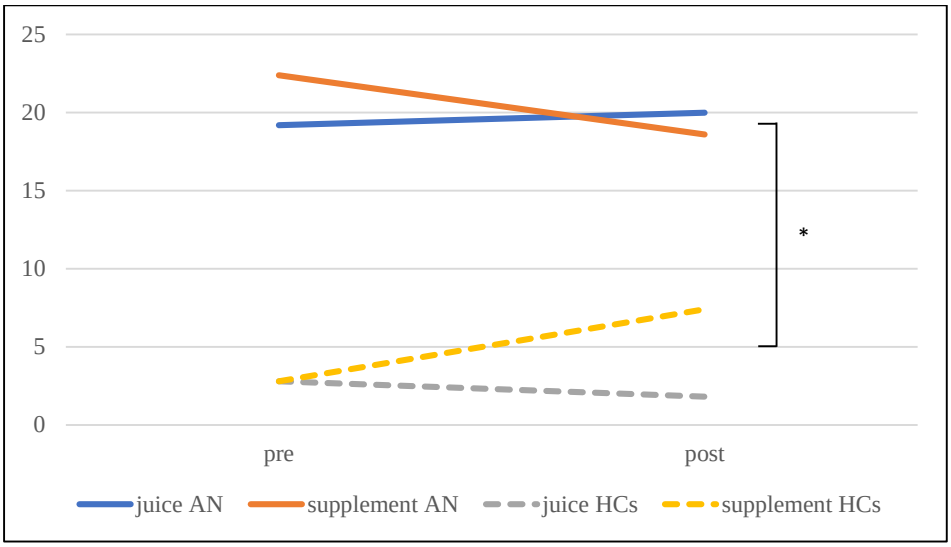

Figure 1d. Need for physical acitvity was significantly different between groups and a significant interaction time*group emerged. Range of mean scores: 11.4 – 43.8.

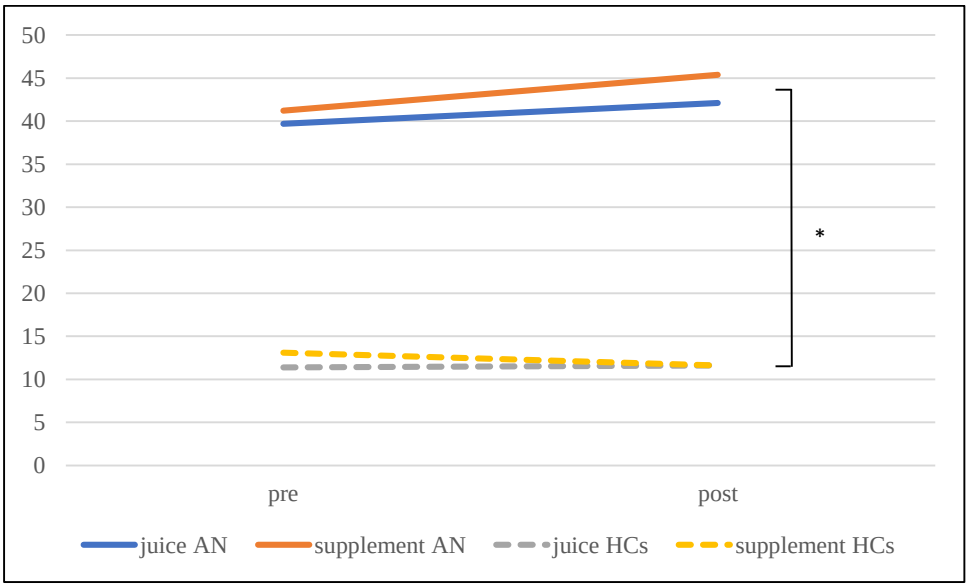

Figure 1e. Restraint was significantly different between groups. Range of mean scores: 3.4 – 38.6.

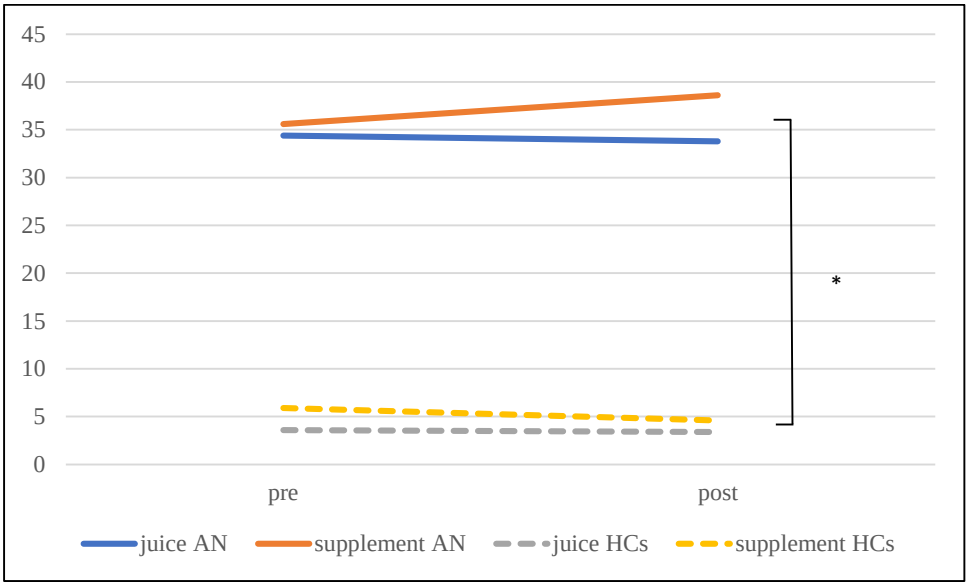

Figure 1f. Satiety was significantly different between groups and a significant effect of time (i.e., before and after the experiment) emerged. Range of mean scores: - 19 – 34.7.

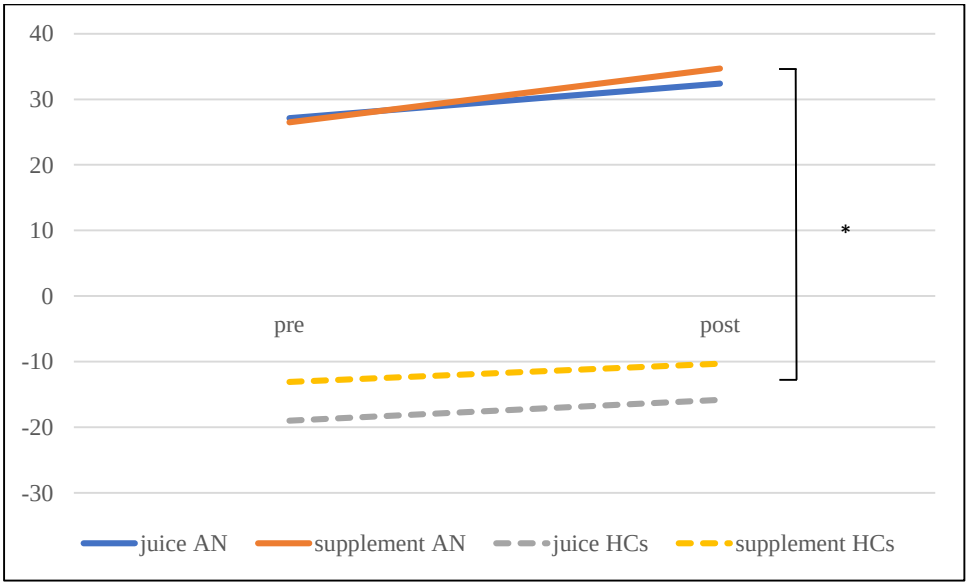

Figure 2. Assessments of patients with anorexia nervosa (AN) and healthy controls (HCs) after the tasting experiment.

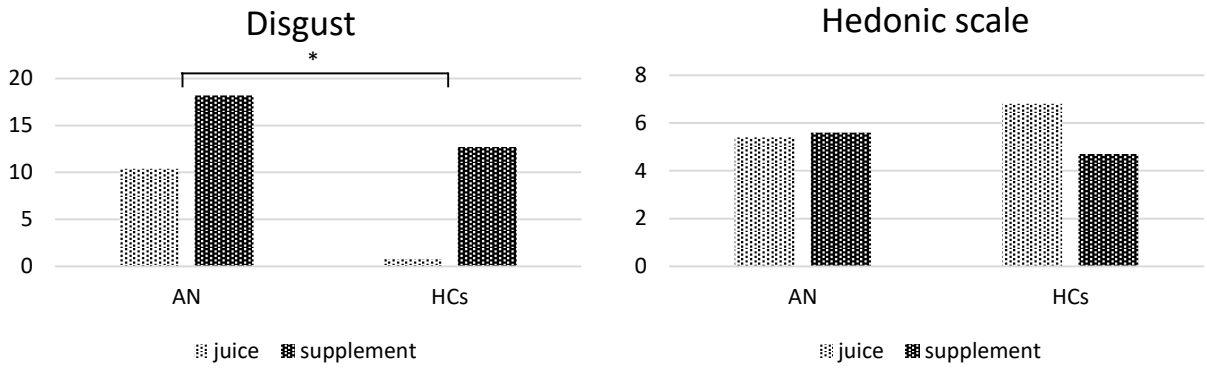

Table 1. Comparison of disgust and reward-based eating between patients with anorexia nervosa (AN) and healthy controls (HCs).

	Patients with AN n=33		HCs n=39		Test statistics	
	Mean(SD)	N(%)	Mean(SD)	N(%)	t	p
Age	26.2(10.3)		23.9(2.7)		1.36	0.18
BMI	13.9(1.6)		20.6(2.2)		14.44	**<0.001**
Duration of illness, years	7.8(8.6)		-		-	-
Education level						**<0.001***
≤ 8 years		12(36.4)		0(0)		
≤ 13 years		9(27.3)		7(17.9)		
> 14 years		12(36.4)		32(82.1)		
Employment						0.235*
Student		20(60.6)		29(74.4)		
Employed		7(21.2)		9(20.5)		
Unemployed		6(18.2)		2(5.1)		

EDE-Q				
Total score	3(1.9)	0.9(0.9)	6	**<0.001**
Restraint	2.6(2)	0.9(1.1)	4.4	**<0.001**
Preoccupation with food	2.6(1.9)	0.5(0.8)	6.3	**<0.001**
Preoccupation with shape	3.8(2.1)	1.3(1.2)	6.2	**<0.001**
Preoccupation with weight	3(1.9)	0.9(1.1)	5.8	**<0.001**
Disgust scale				
Core	29.5(8.6)	31.2(7.2)	0.96	0.338
Animal-reminder	17.6(8)	19.7(5.9)	1.31	0.194
Contamination	10.5(4.6)	8.9(3.5)	1.68	0.096
Total	57.2(17.9)	59.8(14)	0.71	0.478
Reward-based eating scale	15.2(8.3)	9.2(6.6)	3.48	**0.001**

* Fisher's exact test

Table 2. Correlations between disgust scale, reward-based eating scale, and eating psychopathology

	EDE-Q Total	EDE-Q Restraint	EDE-Q Preoccupation with food	EDE-Q Preoccupation with shape	EDE-Q Preoccupation with weight
Disgust scale					
Patients with AN	-.046	-.063	.087	-.079	-.064
HCs	.21	.1	.253	.22	.21
Reward-based Eating Scale					
Patients with AN	**.51****	.27	**.633****	**.484****	**.468***
HCs	.05	.18	-.09	.019	.017

****<0.01**

Table 3. Differences between AN and HCs over time and across conditions.

	Patients with AN n=33		HCs n=39		Effect of time			Effect of condition			Condition*group			Time*group			Effect of group		
	pre Mean(SD)	post Mean(SD)	pre Mean(SD)	post Mean(SD)	F	p	η^2	F	p	η^2	F	p	η^2	F	p	η^2	F	p	η^2
Anxiety					.47	.49	.007	15.07	**<.001**	.18	3.78	.056	.05	.03	.86	.001	19.78	**<.001**	.22
juice	21.5(25.2)	19.4(27)	4.5(6.3)	4.3(6.5)															
supplement	28.3(27.3)	29.5(31.4)	7.9(10.2)	6.5(8.7)															
Hunger					5.7	**.019**	.08	.09	.77	.001	.3	.58	.01	.009	.92	.001	15.97	**<.001**	.19
juice	12.7(19.6)	12.9(20.8)	30.1(20.3)	27.3(21.7)															
supplement	15.1(20.4)	9.5(17.2)	31.8(21.3)	28.7(21)															
Confusion					.009	.92	<.001	1.57	.21	.02	.41	.52	.006	1.31	.26	.018	16.6	**<.001**	.19
juice	19.2(26.4)	20(25.2)	2.8(8.5)	1.8(4.9)															
supplement	22.4(29.8)	18.6(27.5)	2.8(6.8)	7.4(17.7)															
Physical activity					2.34	.13	.03	1.2	.28	.02	.24	.62	.003	5	**.03**	.07	19.4	**<.001**	.22
juice	38.5(35)	40.3(36.5)	11.4(21.6)	11.6(21.7)															
supplement	39.4(31.8)	43.8(35.8)	13.1(22)	11.6(21.1)															
Restraint					.1	.75	.002	1.88	.17	.03	.14	.71	.002	1.52	.22	.02	34.8	**<.001**	.33

juice	34.4(31.3)	33.8(33.8)	3.6(11.3)	3.4(11.3)															
supplement	35.6(33.5)	38.6(32.6)	5.9(15)	4.6(11.4)															
Satiety					11.4	**.001**	.14	1.97	.16	.03	1.1	.3	.01	1.66	.2	.02	50.5	**<.001**	.42
juice	27.1(33.7)	32.4(38.7)	-19(19)	-15.8(22.7)															
supplement	26.5(31.5)	34.7(35.4)	-13.1(26.9)	-10.3(26)															
Disgust					N/A			19.2	**<.001**	.21	0.9	.35	.01	N/A			4.4	**.04**	.06
juice	---	10.4(18)	---	0.77(3.3)															
supplement	---	18.2(24.6)	---	12.7(19.8)															
Hedonic scale					N/A			17.9	**<.001**	.2	23.6	**<.001**	.25	N/A			.41	.52	.006
juice	---	5.4(2.3)	---	6.8(1.4)															
supplement	---	5.6(2.2)	---	4.7(1.9)															

Legend: Confusion: confusion about internal states; physical activity: urge to over-exercise.

Ethical statement

The Ethical Committee of the Department of Neuroscience of the University of Turin, Italy, approved this study and all participants provided their written informed consent.