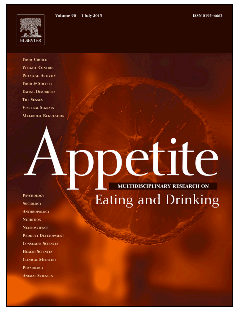
Accepted Manuscript



Computerized measurement of anticipated anxiety from eating increasing portions of food in adolescents with and without anorexia nervosa: Pilot studies

H.R. Kissileff, J.M. Brunstrom, R. Tesser, D. Bellace, S. Berthod, J.C. Thornton, K. Halmi

PII: S0195-6663(15)30103-3

DOI: 10.1016/j.appet.2015.11.026

Reference: APPET 2778

To appear in: *Appetite*

Received Date: 13 January 2015

Revised Date: 20 November 2015

Accepted Date: 22 November 2015

Please cite this article as: Kissileff H.R., Brunstrom J.M., Tesser R., Bellace D., Berthod S., Thornton J.C. & Halmi K., Computerized measurement of anticipated anxiety from eating increasing portions of food in adolescents with and without anorexia nervosa: Pilot studies, *Appetite* (2015), doi: 10.1016/j.appet.2015.11.026.

Title: Computerized measurement of anticipated anxiety from eating increasing portions of food in adolescents with and without anorexia nervosa: Pilot studies

Authors:

H. R. KISSILEFF[1,4], J. M. BRUNSTROM[2], R. TESSER[3], D. BELLACE[3],

S. BERTHOD[3], J.C. THORNTON[1], K. HALMI[3],

[1] Mt. Sinai -St. Luke's/Roosevelt Hospital, NY, NY USA

[2]University of Bristol, Bristol, UK,

[3]Weill Cornell Medical College, White Plains NY USA.

[4] New York Nutrition Obesity Research Center, Departments of Medicine and Psychiatry, Columbia University Medical Center

Address of corresponding author:

1150 St. Nicholas Ave.

New York, NY 10032

Email for corresponding author: hrk2@columbia.edu

"Not for publication", the telephone and fax numbers (with country and area codes)

+1-212-851-5133 (phone) +1-212-851-5579 (fax)

Running head: Anxiety from portion size in anorexia nervosa

Highlights

- A computer program measured expected anxiety from foods in adolescents
- Expected anxiety was larger for those with anorexia nervosa (AN) than controls.
- Maximum tolerated portion was smaller for those with AN compared to controls.
- Expected anxiety and maximum tolerated portion were inversely correlated.
- Expected anxiety was predicted from severity of illness in adolescents with AN.

.

Abstract

Dieting and excessive fear of eating coexist in vulnerable individuals, which may progress to anorexia nervosa [AN], but there is no objective measure of this fear. Therefore, we adapted a computer program that was previously developed to measure the satiating effects of foods in order to explore the potential of food to induce anxiety and fear of eating in adolescent girls. Twenty four adolescents (AN) and ten healthy controls without eating disorders rated pictures of different types of foods in varying sized portions as too large or too small and rated the expected anxiety of five different portions (20-320 kcal). Two low energy dense (potatoes and rice) and two high energy dense (pizza and M&Ms) foods were used. The regression coefficient of line lengths (0 to 100 mm) marked from “No anxiety” to ”this would give me a panic attack”, regressed from portions shown, was the measure of “expected anxiety” for a given food. The maximum tolerated portion size [kcal] (MTPS), computed by method of constant stimulus from portions shown, was significantly smaller, whereas the expected anxiety response was greater, for all foods, for patients compared to controls. For both groups, expected anxiety responses were steeper, and maximum tolerated portion sizes were larger, for low, than high, energy dense foods. Both maximum tolerated portion size and expected anxiety response were significantly predicted by severity of illness for the patients. Those who had larger maximum tolerated portion sizes had smaller anticipated anxiety to increasing portion sizes. Visual size had a greater influence than energy content for these responses. This method could be used to quantify the anxiety inducing potential of foods and for studies with neuro-imaging and phenotypic clarifications.

Key Words: Eating disorders; Portion size selection; Anxiety; Food intake controls; Perception; Food choice

Introduction

Patients with Anorexia Nervosa (AN) are extremely fearful of any attempt to encourage weight gain, and they are noted for denial of many of their symptoms (Halmi, 2007). The creation of a non-threatening objective test to measure the extent of their fearfulness/anxiety specifically towards food would be a most helpful assessment of the patients' conditions before, during, and after treatment. Therefore this study was undertaken to develop methods to generate these measurements and as such is the first study, we know of, to do so.

Clinicians and family members have observed over many decades that patients with anorexia nervosa (AN) are preoccupied with the calorie content and portion size of foods (Halmi, 2007). There is also functional evidence (Ellison et al., 1998) that patients with AN have a fear of eating high-calorie foods, which may be characterized as a food phobia (Kleinfeld, Wagner, & Halmi, 1996). Hence, these observations provide the rationale for regarding AN in part as a food phobia and developing new cognitive-behavioral techniques for treating AN. Although many aspects of eating behavior, food preferences and aversions have been systematically studied in AN patients, there are surprisingly few studies comparing visual presentation of portion sizes and the energy density of foods on anxiety responses. However, two studies suggest that patients with anorexia perceive small portions of food to be larger than controls do (Milos et al., 2013), and rated energy dense food items 12% larger compared to controls' perceptions (Yellowlees, Roe, Walker, & Ben-Tovim, 1988).

In related studies, anxiety ratings were elicited in AN patients with pictorial stimuli of food, but not to food-word stimuli (Nikendei et al., 2008). The authors suggested that the patients concentrated more on the physical features of pictures than on semantic information. Previous studies demonstrated that AN patients dislike high-fat foods and often avoid high carbohydrate foods while preferring sweet taste (Drewnowski, Pierce, & Halmi, 1988; Drewnowski, Halmi, Pierce, Gibbs, & Smith, 1987; Nikendei et al., 2008; Sunday, Einhorn, & Halmi, 1992).

Since cooperation and compliance with assessments and treatment are common problems with AN patients (Crisp & Kalucy, 1974) we thought it worthwhile to devise a measurement in which patients would readily engage and would also indicate an anxiety response to both the energy density and portion size of foods commensurate with severity of illness. We adapted the computerized tasks developed by Brunstrom (Brunstrom, Shakeshaft, & Scott-Samuel, 2008; Brunstrom & Rogers, 2009) so that instead of matching portions for equivalence of satiation, portions were matched in the participant's mind for the maximum that participants could tolerate eating without distress, and that portion was designated the "maximum tolerated portion size (MTPS)" (see also "methods" for further explanation). In addition we measured expected anxiety responses with a computerized visual analog scale as portion sizes increased using foods with different energy densities and nutrient compositions.

We expected that patients would choose smaller MTPSs and show increased expected anxiety as portions increased than controls, and that high energy dense foods would drive expected anxiety higher, and portion size lower, than low energy dense foods, per unit energy, in patients compared to controls. Because these were pilot studies, we could not determine effect size or variability, and therefore we could not set power level in advance, but we report these with statistical inference to demonstrate the potential of the methods, and to provide sufficient data for verification in future studies. Any significance level should be interpreted mainly as a potential testable hypothesis for the future.

Methods

Participant selection: Twenty-three females and one male (identified as letter "D" on Figures 3 and 4) with AN between the ages of 12-18 were recruited from a concurrent NIH Family Therapy Study (Principal Investigator- KH) and the Outpatient Services of the Westchester Division of the New York-Presbyterian Hospital, between October 2, 2008 and June 16, 2010. All patients met DSM-IV (the manual in use at that time) diagnosis for AN determined by the Structured Clinical Interview (First, Gibbon, Spitzer, & Williams, 1996) administered by a PhD Clinical psychologist trained and approved in the assessment for the NIH study. Ten healthy adolescent controls (two males, identified with letters "a" and "e" on Figures 3 and 4) with an average age of 14.6 $\pm$ 2.63 were obtained between August 16, 2010 and January 22, 2012, from community news advertisements and determined free of DSM-IV diagnostic criteria by a structured interview from a MA psychologist, trained and certified for the DSM-IV interview (First et al., 1996).

Informed consent and assent for minors was obtained in written form from all potential participants and their parents. The study was approved by the Institutional Review Board of Weill-Cornell Medical College.

Assessment : The Yale-Brown-Cornell Eating Disorder Scale (Mazure, Halmi, Sunday, Romano, & Einhorn, 1994) was used to assess the severity of eating disorder symptomatology. This scale is based on the structure and format of the Yale-Brown Obsessive-Compulsive Scale, which assesses type and severity of obsessive-compulsive symptomatology. The YBC-EDS is a semi-structured, clinician-administered interview. Four scores are obtained from the YBC-EDS: preoccupations, rituals, total (the sum of preoccupations and rituals scores), and motivation to change (the sum of the resistance, insight, and desire for change scores for both preoccupations and rituals). The YBC-EDS was selected as an assessment in this particular study because it is a good indicator of participant stress and anxiety level. Many questions relate specifically to anxiety level associated with typical eating disorder preoccupations, as well as related anxiety, if prevented from performing eating disorder rituals. Nevertheless it does not assess anxiety, per se. Rather, it is a comprehensive measure of many factors besides food preoccupations and rituals contributing to illness severity in AN, and to motivation to change. Both current and highest experienced severity were recorded, but only the current severity is reported in this paper. Recent studies revealed that the YBC-EDS predicts treatment completion (Halmi et al., 2005) and post-treatment relapse (Halmi et al., 2002).The sensitivity of the YBC-EDS to changes after psychotherapy was established when its scores were significantly different in those with good versus poor global outcome after therapy (Jordan et al., 2009).

The YBC-EDS was not given to controls because we were only interested in determining whether severity of illness in the AN as measured on the YBC-EDS could predict behavior responses to maximum tolerated portions and increasing expected anxiety to increasing portions. Also we did not want to introduce the controls to many of the signs and symptoms of AN that are present on the YBC-EDS, for fear that this might alter their responses or upset them in some way. Furthermore in persons without ED as determined by interview, it is rare to find any pathology on the YBC-EDS (Mazure et al., 1994).

Overall procedure: Four categories of pictured foods were tested based on findings from previous investigations of AN patients food cognitive sets and preferences. We compared energy-dense high fat foods (See Table 1 for composition and energy density of foods pictured) with and without sweet taste (M&M's and Pizza) with bland tasting high carbohydrate, less energy-dense foods (potatoes & rice). These foods are also common components of the American diet.

Insert Table 1 Here

Participants were positioned in front of a computer screen and asked to participate in the following tasks, which were conducted in the order stated below. There were short breaks between each task so that the experimenter could explain them to the participant.

The order of food presentation within tasks was randomized for all tasks except MTPS for which the order was counterbalanced by means of Latin Squares for each group of four participants. Each task for a particular food was completed before the next food was shown. For ideal and typical portion size tests each food was shown twice, once starting with display of the largest portion, the second time starting with the smallest in random order:

Maximum tolerable portion size: This variable was measured using a variant of the method of constant stimuli (previously developed at The University of Bristol (Brunstrom et al., 2008). In this version participants were shown a picture of the same food over 56 trials on a computer screen. The portion size of the food changed according to an algorithm described below as the participant responded to the question: "**Imagine you were going to eat ALL of this food. Would this portion be too big for you to tolerate eating it? Press the RIGHT key if YES the LEFT key if NO".** From the probability "yes" of the response distribution as portion size increased (i.e. a psychophysical function), the 50% point was defined as the point of subjective equality (PSE, see Figure 1 in Brunstrom, et al., 2008) i.e. the participant was ambivalent, and that point was called the "maximum tolerable portion size"). See "data analysis" for details. In the future this instruction should be clarified by adding the words "without purging or compensatory behavior", since this is what we meant.

It is important to note that this classic psychophysical procedure has many advantages over a simple method of adjustment (i.e. moving a cursor until the selected portion appears). Although the latter is quicker, the calculation of a PSE, based on a relatively large number of responses, is likely to be more accurate. It also enables the calculation of an estimate that is not limited by the step size between images. In addition, people often find discrimination tasks (too large or too small?) much easier than estimation tasks and so this approach enables us to derive a precise estimate of a threshold without the need to relying on the participant to explicitly identify one. For example, when asked about willingness to pay, people are very comfortable responding to the question “would you pay X amount? (Y/N)”. However, they find the question “What is the maximum you would pay?” much more difficult. By using our method, based on the calculation of a PSE, we can get around this problem and derive a precise estimate of the maximum based on a set of simple binary decisions.

To improve the efficiency of the method of constant stimuli, the Adaptive Probit Estimation (APE) algorithm (Watt & Andrews, 1981) was employed. With this approach, only a subset of the range of portion sizes was tested. For each of the four test foods, the total number of trials was broken into a series of blocks. Each block comprised a small number of trials (eight trials in the present study). Four stimulus levels were used in each block and these were determined by a rapid and approximate probit analysis of responses during the preceding block. In each case, stimulus levels were selected based on previous responses in order to maximize the information gained about the PSE. In practice, this meant that at the beginning of the session, values were selected at the extremes of the range of portion sizes. Over successive blocks, the range of values decreased, and their average value tended to correspond ever more closely with a participant’s PSE.

Each participant completed a single set of trials that generated a psychophysical function for each food. A trial with each of these four test foods was presented in turn, and this process was then repeated 55 times (56 times in total; 56 x 4 = 224 trials in total). This part of the test session took approximately 10 min to complete, (2.5 min per food) and the participants were invited to take a break after completing half of the trials. The APE routine and the code for presenting the stimuli were both written in Matlab (version 12). The graphical interface was implemented using the Cogent graphics toolbox (developed by John Romaya at the LON at the Wellcome Department of Imaging Neuroscience, UK).

Expected anxiety response to food: To complement the measure of maximum tolerable portion size, we assessed the specific level of expected anxiety associated with the prospect of consuming different portions of food. During each trial, one of the four test foods was presented from one of five portion sizes which doubled (i.e. evenly log spaced) at each step beginning at 20 kcal (i.e., 20, 40, 80, 160, 320 kcals). During each trial, the participant was asked to respond to the question **"How stressful would it be for you to consume this food?"** and to mark a horizontal line with anchors at the far left end of the line, that read **"No anxiety at all,"** and on the far right of the line that read "**This would give me a panic attack."** Fear and stress that are related to food and eating in anorexia nervosa patients are expressed with anxiety. Anxiety is highly correlated with many stressors in these patients and is an emotion they readily describe and use interchangeably with fear and stress (Steinglass & Parker, 2011; Frank et al., 2011). We are using "expected anxiety responses" to reflect the expected anxiety induced by the prospect of eating increasing portions of foods in the graphs and tables as a measure of expected anxiety. The slope of the response regressed from the size of the portion ("stress-slope") was considered a measure of expected anxiety. Thus, an indication of the expected anxiety-inducing potential of a food was derived from the slope of the response level as the portion size increased (see data analysis for details).

Hunger, fullness and time of last meal: Participants indicated on the computer screen when they last ate and rated their current hunger and fullness on 100 mm lines anchored by "not at all" on the far left and "extremely" on the far right. In addition an ANCOVA was conducted for MTPS and stress slope with hunger as the covariate.

Data Analysis: 1. Derived Variables a) *Maximum tolerable portion size*: Participants' responses to the maximum tolerable portion size task were used to determine the specific portion size above which the participants would not tolerate. By means of probit analysis a sigmoid function was fit to the data from which a "Point of Subjective Equality" (PSE) was derived (Brunstrom et al., 2008). The PSE represents the point at which the "yes" response to the question "**Would this portion be too big for you to tolerate eating it?"** was selected 50% of the time. In this way, a measure of maximum tolerable portion size was extracted.

b) *Expected* Anxiety *slope:* For expected anxiety response across portions of foods shown, we used the slope (i.e. regression coefficient) of the expected anxiety response per log kcal of food shown, obtained by simple linear regression of the expected anxiety response against the log (portion size) in kcal for each subject's response across the five portions shown for each food. The stress slopes were then compared in the same manner as the maximum portions sizes, by ANOVA as described below.

2) Statistical Analysis A mixed model ANOVA with repeated measures on participants, using SAS versions 9.2, 9.3 and 9.4 proc Mixed method = type3, was conducted for each dependent variable (i.e. maximum tolerable portion size shown and stress response slope) in which independent fixed factors were food (4 levels), and group (2 levels). Planned comparisons were conducted to assess the pattern of differences between groups for foods as well as interactions.

To determine whether MTPS was related to stress slopes, and if so, were there differences in this relationship among foods and between groups, separate regressions were run for each group and food. This was followed by an ANCOVA with MTPS as dependent variable, stress slope as covariate, and food and group as independent classification (i.e. fixed) variables.

We used regression analysis, in the patients only, to determine whether MTPS and stress slope in separate models were predicted by severity of illness, measured by the YBC-EDS score, and body mass index (BMI) for each food separately as well as for all foods combined. Initially, the models included food x BMI and food X YBC-EDS score interactions, and where these were not significant, they were dropped and only the overall regressions are reported. We also regressed MTPS from stress-slope to determine whether MTPS was related to expected anxiety. We regressed YBC-EDS score from BMI to determine whether severity of illness from an anxiety related measure corresponded with body size.

Results

Participant characteristics and preliminary analyses (See Table 2): The participants, anorectic-restrictors (21) and anorectic-binge-purgers (3) did not differ on any of the measured demographic variables and thus were combined for all analyses. The control persons did not differ in age but had a higher BMI and current weight than did the AN patients. YBC-EDS scores indicated a range of preoccupation and rituals from mild to severe. Males' data shown in figures 3 and 4 were not visibly different from females, although the paucity of data prevented a proper analysis for gender difference.

Insert Table 2 Here

---

*Maximum Tolerated Portion size (*MTPS)*:* There were significant main effects for both group (F(1,.89) = 9.93, p = .0037) and food (F(1,89) = 17.21, p <.0001) but no significant food x group interaction for MTPS. Nevertheless, MTPS was significantly smaller for patients than for controls for the high, but not low, energy dense foods (see Figure 1). The mean MTPS for the high energy dense foods (pizza and M&Ms) compared to low energy dense (rice and potatoes) was 115 kcal (± 56 SE, t (89) = 2.05 , p = .04) higher for controls than for patients.. Inspection of the pictures in Figure 1 representing the mean MTPSs indicated that they were very similar in physical size across foods, and smaller in patients than controls. If participants were selecting portions based on their physical size, rather than their energy content, pictures of the same size would have different energy content, thereby explaining the otherwise unexpected reversal of our prediction that larger portions would be chosen from “safe”, low energy dense foods. Differences in MTPS (in kcal) between foods depended strongly on the energy densities of the foods. The farther apart the foods were in energy density (see Table 1 for energy densities) the greater was the difference in MTPS. For example, M&Ms and potatoes are farthest apart in energy density and MTPS, whereas potatoes and rice are closest in both energy density and MTPS.

Insert Figure 1 here

Expected Anxiety slope (= “stress-slope” for short): As the portion shown increased, the expected-anxiety response increased for all foods (see Figure 2) with significant differences among the food (i.e. food effect: F = 30.41(3,96), p <.0001), and a significant difference between patients and controls (i.e. group effect: $F = 16.31(3,32)$, $p<.0003$), but no food x group interaction. Patients' slopes were significantly greater than zero and significantly higher than slopes in controls averaged across foods, and for each food. Controls' slopes were significantly different from zero only for rice and potatoes (see Table 3 for means and differences of stress-slopes between groups by food, and Table 4 for differences in stress-slopes between foods collapsed across groups, because the interaction was not significant). As was the case for MTPS, it appears that participants were attending to the actual size, rather than the energy content of the portion. Potatoes and rice had significantly higher slopes (55.92 mm/log kcal ± 3.96 SE, 51.24 ± 3.98, respectively) than Pizza and M&Ms (30.96 ± 4.5, 27.41 ± 4.2, respectively), but within each grouping there was no significant difference.

The pattern of differences across foods was opposite to that seen in MTPS selection, i.e. stress-slopes were less steep as the energy density increased, whereas MTPS increased with energy density. When means for high and low energy dense foods were combined for both groups, there was a significant difference in slopes (21.4 mm/log kcal ± 2.3 SE, t, 96 df, 9.33, $p<0.0001$) between the two high energy dense foods combined (M&Ms and Pizza, M = 19.2 ± 3.1 SE) and the two low energy dense foods combined (Potatoes and Rice, M = 40.7 4 mm/log kcal ± 3.1 SE).

Insert Tables 3 and 4 and Figure 2 here

Hunger fullness and time since last meal: For the patients, mean hunger rating was 22.4 mm ± 5.0 and mean fullness was 43.6 mm ± 5.2 SE. Mean time since last meal was 5.3 h ± 1.3. For controls mean hunger rating was 49.5 ± 8.1 and mean fullness was 38.1 mm ± 8.0 SE. The significant difference between patients' and controls' hunger was 27.0 mm ± 9.6 SE, (t (32) = 2.8, p = 0.0086). The time since last meal was 7.5 h ± 2.0 SE for controls and 5.3 h ± 1.3 SE for patients. Neither MTPS nor stress slope was affected by the ANCOVA adjusting for hunger. However, there was a significant regression of MTPS from hunger for rice in patients only (b = 5.14 kcal/mm± 1.24 SED, p = 0.0005).

Relationship of severity of illness and BMI with stress-slope and MTPS in patients with AN: The steepness of the stress-slope increased significantly with increasing severity of illness, measured by YBC-EDS score for all foods (see Figure 3). That is, the more severely ill the patient, the greater was the increase in stress response as portion size increased. The interaction of food with YBC-EDS score was significant for stress slopes (F = 17.28, 4,88 df, p <.0001), indicating there were significant differences in the stress slope--YBC-EDS score regressions among foods For stress slope regressed from BMI the BMI x food interaction was not significant (p = 0.1139), but the overall regression with all foods combined was (b = -.361 (mm/kcal)/(M/kg^2), p = .023). For MTPS there was an interaction between food and YBC-EDS score (F = 21.42, df = 4,87, p <0001), but the regressions of MTPS from YBC-EDS score were significant only for the two high energy dense foods (p's <.0001), pizza (b = -35.5 kcal//(M/kg^2) and M&M's (b = -18.8 kcal//(M/kg^2). The regression of MTPS from BMI, like YBC-EDS score, had a significant interaction between food and BMI (p = 0.002), but the only significant regression of MTPS from BMI was for M&M's (b = 117.5 ± 30.5, p =0.0002). Although BMI has been included as potential indicator of severity of illness, it should be noted that BMI was <u>not a good indicator of severity of illness for two reasons</u>: First, BMI had a much lower coefficient of variation than YBC_EDS, (CV = 7%, whereas the CV for YBC_EDS is 65%), and second, BMI and YBC-EDS didn't correlate (r-square = 0.03, p = 0.364).

Duration of illness, another potential indicator of severity of illness was not available for each subject for this paper, but ranged from 3 mo to 2 yr. However, duration of illness is not necessarily related to severity of illness at a point in time.

Insert Figure 3 here

Maximum tolerable portion size predicted by stress-slope: In the patients, for all foods except rice the maximum tolerable portion size was significantly predicted from the stress-slope (see Figure 4 and Table 5 for statistics on slopes and their SE's for each food). The regression coefficients (i.e. slopes) of this relationship for different foods also differed significantly from one another ($F_{4,83}$ = 15.75 for the slope x food interaction) in the same pattern as did the MTPSs. Foods closest in energy density (potatoes and rice, M&Ms and pizza) did not differ from each other, but all other differences among foods were significant. For the controls, unlike the patients, the slopes of the relationship of maximum tolerable portion and stress-slope were not significantly different from zero for any food.

Insert Figure 4 and Table 5 here

Discussion

Novelty and utility: This paper demonstrates that new computerized portion-selection paradigms (i.e. maximum tolerable portion size and stress slope as portion sizes increase) could become a useful objective clinical adjunct for assessment of expected anxiety induced by food in patients with Anorexia Nervosa. Because it is not easy to measure anxiety in general (e.g see (Spielberger & Reheiser, 2009)) and we could not find any quantitative measures of food-related anxiety in particular, these paradigms could provide quantitative assessment that is currently lacking and could also be used to test food-related anxiety and portion size selection in a broad range of eating disorders and situations including those of bulimic and obese patients. It is also notable that this technique of selecting portion sizes based using the method of food choices, similar to methods used here, has been shown to be robust for measuring factors that affect a person's food choice under certain conditions and reflects a person's eating behavior on a daily basis. For example, it was found in a study (Brunstrom & Rogers, 2009) that high energy-dense foods are selected in larger portions because they are expected to be less satiating rather than because of their palatability using the aforementioned technique. Nevertheless, it should be kept in mind that this is a pilot study and any statistical statement will need confirmation in a follow up.

AN patients tolerate smaller portion sizes than controls: Interestingly, this was only significant for the high energy dense foods pizza and M&Ms (Figure 1). AN patients are quite knowledgeable of the calorie content in foods and are preoccupied with calorie counting (Halmi, 2007) which may be partly responsible for their inability to tolerate large portions of high energy dense foods. Additionally, AN patients have demonstrated an altered perception of portion sizes and tend to overestimate the size that is presented to them, specifically with foods that have a high caloric density (Milos et al., 2013; Yellowlees et al., 1988). Thus, if the portion size is overestimated, the patients may automatically shift tolerance towards a smaller portion of that food.

AN patients show greater expected anxiety responses than controls: The expected anxiety response of AN patients for all foods were greater than for controls. Surprisingly, the stress-slope was steeper for the low energy dense foods per log kcal than the high energy dense foods for AN patients. Contrary to expectations based on participants' perceptions of the energy in portions, as opposed to the visual size, the most energy dense foods, such as M&Ms and pizza, induced less expected anxiety per kcal than boiled potatoes and rice. The portion sizes used were chosen on the assumption that energy content would be the primary determinant. However, given the pattern of results, particularly the pattern for the relation of expected anxiety response per kcal and the steeper slopes for the low density, as opposed to high density, foods, it appears that physical size is probably more salient in driving the response than energy content. Although calorie counting and preoccupation with calorie density are commonly observed in AN patients (Halmi, 2007), their response to the visual stimulus of the size of the portion superseded their response to the perceived energy content (Figure 2). This response was also expressed with a greater increase in expected anxiety to increased portion size of potatoes and rice versus pizza and M&Ms. For example, pizza, at 320 kcal, visually occupied the same space on the plate as rice at 160 kcal. Similarly, 160 kcal of pizza appeared to occupy the same space as 80 kcal of rice. Furthermore, it has been noted that AN patients show strong aversion toward high carbohydrate foods (Crisp & Kalucy, 1974) which has been considered “carbohydrate phobia”. This may be another plausible explanation for the greater expected anxiety response per log kcal for the high carbohydrate foods in the study (i.e. rice and potatoes) compared to the energy-dense foods pizza and M&Ms.

Differing responses among foods: The farther apart were the differences in energy density among foods the greater was the difference in maximum tolerated portions for the controls, but not for the patients. This can be seen by observing the energy densities in relation to MTPS in Table 1. This result does not necessarily indicate that energy density was driving the response, because the energy densities are completely confounded in the presentation of the portions, and the response was scaled according to energy content. Consequently if the participants were paying more attention to the physical portions than the energy content, this pattern is exactly what would be predicted, because the same sized portion of any given image will have more energy, if the energy density is higher. The role of physical size vs energy content is currently being explored and the predictions are that to the extent portion sizes are driven by area, not energy, differences among the foods will disappear. Those differences that remain would have to be attributable to other aspects of the food than energy density, such as fat or sugar content. Certainly, it would be important for future studies to explore a greater variety of foods, chosen and calibrated along a variety of dimensions (e.g. weight, volume, energy density, macronutrient composition). Indeed, a recent study (Keenan, Brunstrom, & Ferriday, 2015) found that as within-meal variety increased, expected satiation tended to be based on the perceived volume of food(s) rather than on prior experience.

Stress-slope and MTPS are inversely correlated: For all foods, the stress-slope and MTPS were shown to be inversely correlated with each other (Figure 4). Thus, the more expected anxiety in response to the food cues, the smaller the portion size the patient is able to tolerate. Therapeutically, this information may be of benefit to patients. If the anxiety response were mitigated, the patient would theoretically be able to tolerate more food. This result is important because it demonstrates that the two responses are measuring the same underlying problem, i.e. expected anxiety from eating the portion.

Stress-slope is predicted from severity of illness: Severity of illness significantly and positively predicted the increase in expected anxiety produced by increasing portion sizes of all foods studied (Figure 3). Thus, this technique could be very useful in a clinical setting in further characterizing the disease and efficacy of treatment for patients. It is important to note that the correlation between expected anxiety slope and the YBC-EDS score is not simply attributable to the fact the two scores are measuring the same thing, anxiety. First of all looking at portions did not induce anxiety per se. Rather it produced an expectation of anxiety, if the participant had to eat the portion. Second in a more recent study (Bellace et al., 2012) with a subset of the YBC-EDS the YBC-EDS-SRQ measured symptoms such as eating rituals and motivation to change, not anxiety. Indeed, the YBC-EDS- SRQ showed no significant correlations between various symptom dimensions of the YBC-EDS-SRQ and the State Trait Anxiety Inventory (STAI), so our findings (prediction of stress slopes from severity of symptoms) is notable. Furthermore, our measure is innovative because it reflects expected anxiety with eating a specific food rather than just general anxiety.

Limitations and Advantages: An advantage to this computerized testing was that all AN patients invited to participate in this study fully cooperated, which is unusual for persons with AN and may be attributable to their being in the moderate range of severity of illness. The use of pictures rather than actual food is both an advantage and a limitation. Since participants were not confronted with actual food, there may be concern that the findings in this study have no relevance to reality. The next step would be to relate this task performance with actual food intake. Given that estimated portion sizes correlate well with what they actually eat in control participants (Wilkinson et al., 2012), it is likely that such would be the case in patients with AN. A third limitation is that there were only three males in the study, and that the number of controls was less than half the number of patients, resulting in greater variability in the controls. However, within the time frame allotted for the study, we were only able to recruit 10 controls. It is notable that all three males' stress slopes (letters "D" "a" and "e" in figures 3 and 4) were at the lower end of the distributions for several of the foods, but that for the other variables their location in the distributions was not remarkable. A fourth limitation is that we did not run the YBC_EDS on the controls. We feel that this is minor concern because the controls were carefully interviewed by the same master's degree psychologist who was trained and certified at Stanford for all the diagnostic adolescent interviews for AN for the NIMH funded family therapy study. Thus we were confident that the controls had no eating disorder behaviors. Of course we would have been closer to absolute certainty if a post interview was conducted. We recommend that future studies employ this scale in controls, just to be sure.

Conclusion: To our knowledge, this interactive computer program is the first to use the method of constant stimuli to measure the MTPS and a simple VAS scaling procedure to measure expected anxiety-inducing capacity (i.e. stress slope) of foods in patients with AN, and it clearly shows they differ from controls. This program could be useful for clinical assessments, measuring change during the course of treatment, and possibly predicting treatment outcome. They could also be used as an adjunct to exposure and response therapy to get severely ill patients to cope with their anxiety about eating. Finally these assessments could also be used in conjunction with neural imaging and genetic testing for understanding neural and genetic bases of the behavioral disturbances, because the behavioral response to portion size has been shown here to be capable of both measurement and manipulation in response to food cues from at least two sources, energy density and physical size. This is a preliminary report, and it is hoped that others will use these procedures with other eating disorders.

Acknowledgements

H.R. Kissileff was supported by the NIH grant (NIH/NIDDK DK26687) during the early work (07-8) on this project, and design and data analysis for this study were conducted as services of the Human Ingestive Behavior Core Laboratory of the New York Nutrition Obesity Research Center, at Mt Sinai-St. Luke's/Roosevelt Hospital, and subsequently at Columbia University Medical Center, F.X. Pi-Sunyer, Director. Jennifer Nasser provided suggestions for the project but did not participate in data collection, analysis or writing. Volunteers Chaya Lieba Berger, and Marshall Curson provided help with the tables, figures and corrections to an previous iteration of this manuscript. Kissileff also thanks Chris Douglas, a master's student at the Columbia University Institute of Human Nutrition for interesting insights and suggestions regarding the effect of energy density on the responses and for technical work on the manuscript, and Musya Herzog, a masters student at Columbia University Teachers College for helpful discussions relating to anxiety and physical portion size and for help with the revisions to the first draft.

Reference List

Bellace, D. L., Tesser, R., Berthod, S., Wisotzke, K., Crosby, R. D., Crow, S. J. et al. (2012). The YaleΓÇÉBrownΓÇÉCornell eating disorders scale selfΓÇÉreport questionnaire: A new, efficient tool for clinicians and researchers. *International Journal of Eating Disorders, 45,* 856-860.

Brunstrom, J. M. & Rogers, P. J. (2009). How many calories are on our plate? Expected fullness, not liking, determines, meal-size selection. *Obesity.(Silver.Spring), 17,* 1884-1890.

Brunstrom, J. M., Shakeshaft, N. G., & Scott-Samuel, N. E. (2008). Measuring 'expected satiety' in a range of common foods using a method of constant stimuli. *Appetite, 51,* 604-614.

Crisp, A. H. & Kalucy, R. S. (1974). Aspects of the perceptual disorder in anorexia nervosa. *British Journal of Medical Psychology, 47,* 349-361.

Drewnowski, A., Halmi, K. A., Pierce, B., Gibbs, J., & Smith, G. P. (1987). Taste and eating disorders. *American Journal of Clinical Nutrition, 46,* 442-450.

Drewnowski, A., Pierce, B., & Halmi, K. A. (1988). Fat aversion in eating disorders. *Appetite, 10,* 119-131.

Ellison, Z., Foong, J., Howard, R., Bullmore, E., Williams, S., & Treasure, J. (1998). Functional anatomy of calorie fear in anorexia nervosa. *Lancet, 352,* 1192.

First, M. B., Gibbon, M., Spitzer, R. L., & Williams, J. B. W. (1996). Structural clinical Interview for DSM-IV Axis I Disorders - Patient Edition. New York, NY: New York State Psychiatric Institute, Biometrics Research.

Frank, G., Roblek, T., Shott, M., Jappe, L., Rollin, M., Hagman, J. et al. (2011). Heightened Fear of Uncertainty in Anorexia and Bulimia Nervosa. *International Journal of Eating Disorders, 66,* 1-6.

Halmi, K. A. (2007). Anorexia nervosa and bulimia nervosa. In I.A.Martin & F. Volkmar (Eds.), *Lewis's child and adolescent psychiatry: A comprehensive textbook* (4 ed., pp. 592-602). New York, NY: Lippincott, Williams and Wilkins.

Halmi, K. A., Agras, W. S., Crow, S., Mitchell, J., Wilson, G. T., Bryson, S. W. et al. (2005). Predictors of treatment acceptance and completion in anorexia nervosa: implications for future study designs. *Arch.Gen.Psychiatry, 62,* 776-781.

Halmi, K. A., Agras, W. S., Mitchell, J., Wilson, G. T., Crow, S., Bryson, S. W. et al. (2002). Relapse predictors of patients with bulimia nervosa who achieved abstinence through cognitive behavioral therapy. *Arch.Gen.Psychiatry, 59,* 1105-1109.

Jordan, J., Joyce, P. R., Carter, F. A., McIntosh, V. V., Luty, S. E., McKenzie, J. M. et al. (2009). The Yale-Brown-Cornell eating disorder scale in women with anorexia nervosa: what is it measuring? *Int.J.Eat.Disord., 42,* 267-274.

Keenan, G. S., Brunstrom, J. M., & Ferriday, D. (2015). Effects of meal variety on expected satiation: evidence for a ΓÇÿperceived volumeΓÇÖheuristic. *Appetite*.

Kleinfeld, E. I., Wagner, S., & Halmi, K. A. (1996). Cognitive-behaviour treatment of anorexia nervosa. *Psychiatr Clin North Am, 19,* 715-737.

Mazure, C. M., Halmi, K. A., Sunday, S. R., Romano, S. J., & Einhorn, A. M. (1994). The Yale-Brown-Cornell Eating Disorder Scale: development, use, reliability and validity. *Journal of Psychosomatic Research, 28,* 425-445.

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.

Nikendei, C., Weisbrod, M., Schild, S., Bender, S., Walther, S., Herzog, W. et al. (2008). Anorexia nervosa: selective processing of food-related word and pictorial stimuli in recognition and free recall tests. *Int.J.Eat.Disord., 41,* 439-447.

Spielberger, C. D. & Reheiser, E. C. (2009). Assessment of emotions: Anxiety, anger, depression, and curiosity. *Applied Psychology: Health and Wellâ€ Being, 1,* 271-302.

Steinglass, J. & Parker, S. (2011). Using Exposure and Response Prevention Therapy to address fear in Anorexia Nervosa. *Eating Disorders Review, 22,* 1-5.

Sunday, S. R., Einhorn, A., & Halmi, K. A. (1992). Relationship of perceived macronutrient and caloric content to affective cognitions about food in eating-disordered, restrained, and unrestrained subjects. *American Journal of Clinical Nutrition, 55,* 362-371.

Watt, R. J. & Andrews, D. P. (1981). APE: Adaptive probit estimation of psychometric functions. *Current Topics in Neuroendocrinology, 1,* 205-214.

Wilkinson, L. L., Hinton, E. C., Fay, S. H., Ferriday, D., Rogers, P. J., & Brunstrom, J. M. (2012). Computer-based assessments of expected satiety predict behavioural measures of portion-size selection and food intake. *Appetite, 59,* 933-938.

Yellowlees, P. M., Roe, M., Walker, M. K., & Ben-Tovim, D. I. (1988). Abnormal perception of food size in anorexia nervosa. *Br.Med.J.(Clin.Res.Ed), 296,* 1689-1690.

Figure legends

Figure 1. Maximum tolerated portion size for patients and controls for each food.

The portions corresponding to each food are shown at the bottom. Letters indicate means that did not differ between patients and controls. There were significant differences in maximum portion for anorectics between potatoes and rice (92.7 kcal ± 42.1, SED p = 0.0301), between potatoes and pizza (105.0 kcal ± 42.6 SED, p = 0..0148, and between M&M's and each of the other foods (potatoes 224.1 kcal ± 42.1, p <.0001), rice (131.3 k cal ± 42.01 SED, p = 0.0024), pizza (118.1 kcal ± 42.62 SED, p = 0.0068) . The corresponding differences for controls were between potatoes and pizza (247 kcal ± 67.2 SED p = 0.0004), rice (142.6 kcal ± 67.2 SED, p = 0.0367) , and M&Ms (325.3 kcal ± 67.2 SED, p <.0001) and between M&Ms and rice (221.0 kcal ± 67.2 SED, p = 0.0015).

Figure 2. Mean stress-slopes for each food.

Left panel show patients, right panel controls. Each line is the mean of the individual slopes and intercepts from each participant for each food. Note that lines connecting points with the same stress level but different energy levels are represented by portions of foods corresponding to these energy levels shown at the bottom. It should be clear that the lines connect portions that are approximately the same physical area, but different in energy content. The smaller comparison (160 kcal pizza = 80 kcal rice) is shown on the left and larger (320 pizza = 160 rice on the right). Note the stress slopes for controls on the right are all lower than for patients. Statistics of all regression lines are shown in Table 5. Axis label for the abscissa is shown in both log and additive units so that the linear log relationship of expected anxiety to energy content is clear in relation to the actual stimulus energy contents.

Figure 3. Stress-slope regressed from YBC-EDS score for patients.

Each panel shows the relationship for each food, and individual participants are shown by the same letter across foods. Axis label for the abscissa is shown in both log and additive units so that the linear log relationship of expected anxiety to energy content is clear in relation to the actual stimulus energy contents. Participants labeled with capital letters “H” “F” and “I” are anorectic-purgers. The lone male is “D”. Regression statistics are tabulated below:

FOOD	INTERCEPT ± SE	P_INT	SLOPE ± SE	SLOPE_PROBT	R-SQUARED
A_POTATOES	39.10 ± 6.18	<.0001	1.51 ± 0.47	0.0040	0.32
D_RICE	30.63 ± 5.44	<.0001	1.85 ± 0.41	0.0002	0.48
I_PIZZA	5.78 ± 5.65	0.3180	2.26 ± 0.43	<.0001	0.56
O_M&M"S	8.30 ± 6.31	0.2020	1.72 ± 0.48	0.0020	0.37

Figure 4. Regressions of maximum tolerated portion size predicted from stress-slope as portions increased.

One panel is shown for each food. Each letter shows the same participant on each plot so the relative positions across foods can be compared. Patients are lower case, solid line; controls are uppercase dotted line. Males are identified with letters “a” and “e” for controls and “D” for patients.

Participant codes are:

a	1	b	2	c	3	d	4	e	5	f	6	g	7	h	8	i	9	j	10	A	11	B	12
C	13	D	14	E	16	F	17	G	18	H	19	I	20	J	21	K	22	L	23	M	24	N	25
O	26	P	27	Q	28	R	29	S	30	T	31	U	32	W	33	X	34	'	80	'	81		

The regression statistics for the foods are as shown in Table 5.

Table 1

Composition of foods shown to participants.

Food type	Carbohydrate (g)	Protein (g)	Fat (g)	Fibre (g)	Total Weight (g)	Portion Range (kcal)	Energy Density (kcal/g)
Potatoes	46	4	0	3	267	20-800	0.75
Rice	40	4	3	0	140	20-800	1.43
Pizza	21	9	9	1	49	20-1200	4.08
M&Ms	22	4	10	1	38	20-1200	5.26

Macronutrient composition (grams) of the 4 food stimuli (values given per 200 kcal)

617 Table 2.

618 Demographic Data

Groups	Controls	AN-R Mean ± SD	AN-P Mean ± SD
Number	10	21	3
Age + SD	14.6 ± 2.63	15.62 ± 1.56	14.33 ± 1.15
Body Mass Index (BMI)	20.6 ± 1.35	17.09 ± 1.39	17.23 ± 1.03
Target Weight	N/A	119.2 ± 12.35	104.67 ± 4.16
Current Weight (lb)	114.7 ± 17.81	100.32 ± 12.50	93.43 ± 8.14
YBC-EDS Score	N/A	11.00 ± 7.31	8.67 ± 7.64

Table 3.
Mean Slopes of Expected Anxiety (i.e. "stress-slopes") as portion size increased shown by group and food

Food	Group					
	Anorectic		Control		Difference (Control-Anorectic)	
	Estimate ± SE (mm/log kcal)	Pr > |t|	Estimate ± SE (mm/log kcal)	Pr > |t|	Estimate ± SED (mm/log kcal)	Pr > |t|
A_Potatoes	55.92 ± 3.76	<0.0001	31.89 ± 5.83	<.0001	-24.03 ± 6.93	0.0008
D_Rice	51.24 ± 3.76	<0.0001	23.59 ± 5.83	0.0001	-27.66 ± 6.93	0.0001
I_Pizza	30.96 ± 3.76	<0.0001	8.77 ± 5.83	0.1355	-22.19 ± 6.93	0.0019
O_M&Ms	27.41 ± 3.76	<0.0001	9.60 ± 5.83	0.1027	-17.81 ± 6.93	0.0118
Z_All foods	41.38 ± 3.08	<0.0001	18.46 ± 4.77	0.0005	-22.92 ± 5.67	0.0003

Note: Letters next to foods are simply identifiers to ensure the coded food names were carried over into the table. P values are for slopes differing from zero. Estimate is the estimated slope from the SAS output.

Table 4.

Differences in stress-slopes between foods, both groups combined.

<table>
<tr><th>Foods</th><th>Difference ± SE
(mm/log kcal)</th><th>DF</th><th>t Value</th><th>Pr > |t|</th></tr>
<tr><td>D-A Rice-Potatoes</td><td>-6.49 ± 3.26</td><td>96</td><td>-1.99</td><td>0.0489</td></tr>
<tr><td>I-A Pizza-Potatoes</td><td>-24.04 ± 3.26</td><td>96</td><td>-7.39</td><td><.0001</td></tr>
<tr><td>I-D Pizza-Rice</td><td>-17.55 ± 3.26</td><td>96</td><td>-5.39</td><td><.0001</td></tr>
<tr><td>O-A M&Ms-Potatoes</td><td>-25.40 ± 3.26</td><td>96</td><td>-7.80</td><td><.0001</td></tr>
<tr><td>O-D M&Ms-Rice</td><td>-18.91 ± 3.26</td><td>96</td><td>-5.81</td><td><.0001</td></tr>
<tr><td>O-I M&Ms-Pizza</td><td>-1.36 ± 3.26</td><td>96</td><td>-0.42</td><td>0.6762</td></tr>
</table>

Note: The critical ranges (i.e. size of the differences in slopes between foods to reach significance), by Duncan test were for 2, 3 and 4 steps apart between mean slopes shown in Table 3, respectively, 7.588, 7.984, and 8.245.

627

Table 5.
Regression line statistics for maximum tolerated portion size predicted from stress-slope shown in Figure 4.

FOOD	DF	INTERCEPT ± SE	INTERCEPT_P	SLOPE ± SE	SLOPE_P	R-SQUARED	Root MSE
Patients							
A_POTATOES	21	223 ± 39.63	0.00001	-1.88 ± 0.67	0.01047	0.27	62.22
D_RICE	21	337 ± 98.77	0.00259	-2.43 ± 1.77	0.18600	0.08	156.97
I_PIZZA	20	617 ± 40.53	<0.0001	-6.04 ± 1.12	0.00003	0.59	102.74
O_M&M"S	21	585 ± 59.51	<0.0001	-8.52 ± 1.71	0.00006	0.54	162.02
Controls							
A_POTATOES	7	233 ± 142.50	0.14606	-1.34 ± 4.01	0.74911	0.02	165.13
D_RICE	7	337 ± 92.96	0.00844	-1.84 ± 3.32	0.59698	0.04	149.43
I-PIZZA	7	715 ± 93.71	0.00012	-7.68 ± 8.07	0.37287	0.11	153.05
O_M&M"S	7	537 ± 116.60	0.00245	-2.13 ± 8.20	0.80231	0.01	229.07

Figure 1

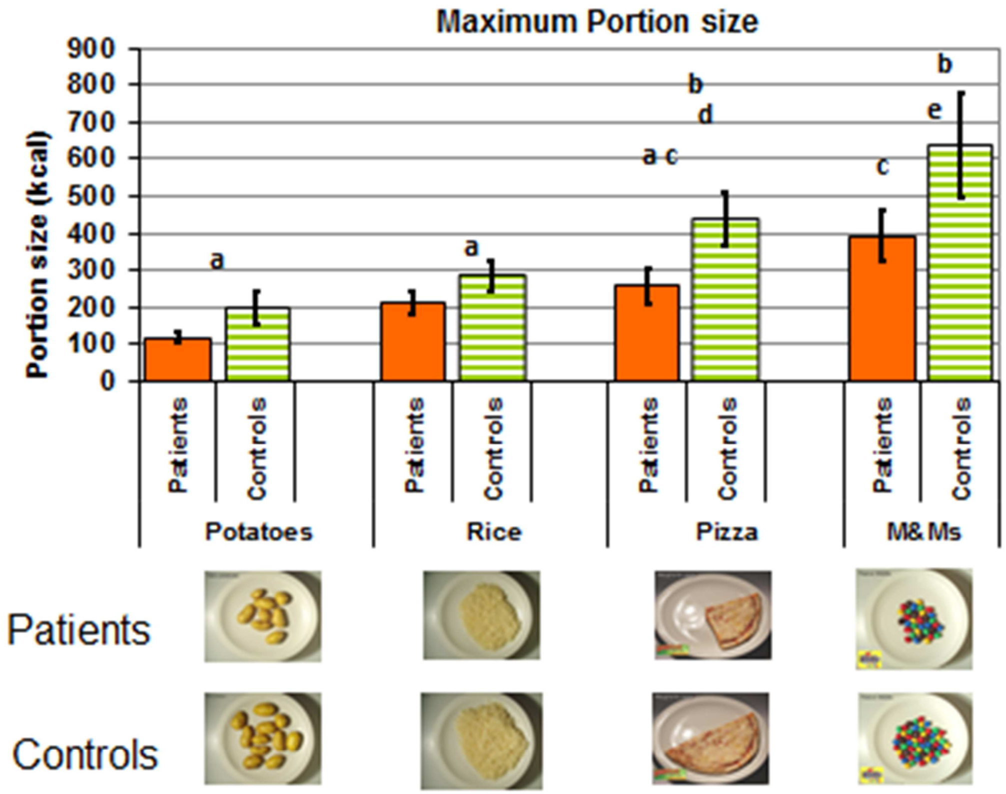

Maximum Portion size
Portion size (kcal)
900
800
700
600
500
400
300
200
100
0
a
a
a c
b
d
c
b
e
Patients
Controls
Potatoes
Rice
Pizza
M& Ms
Patients
Controls

Figure 2

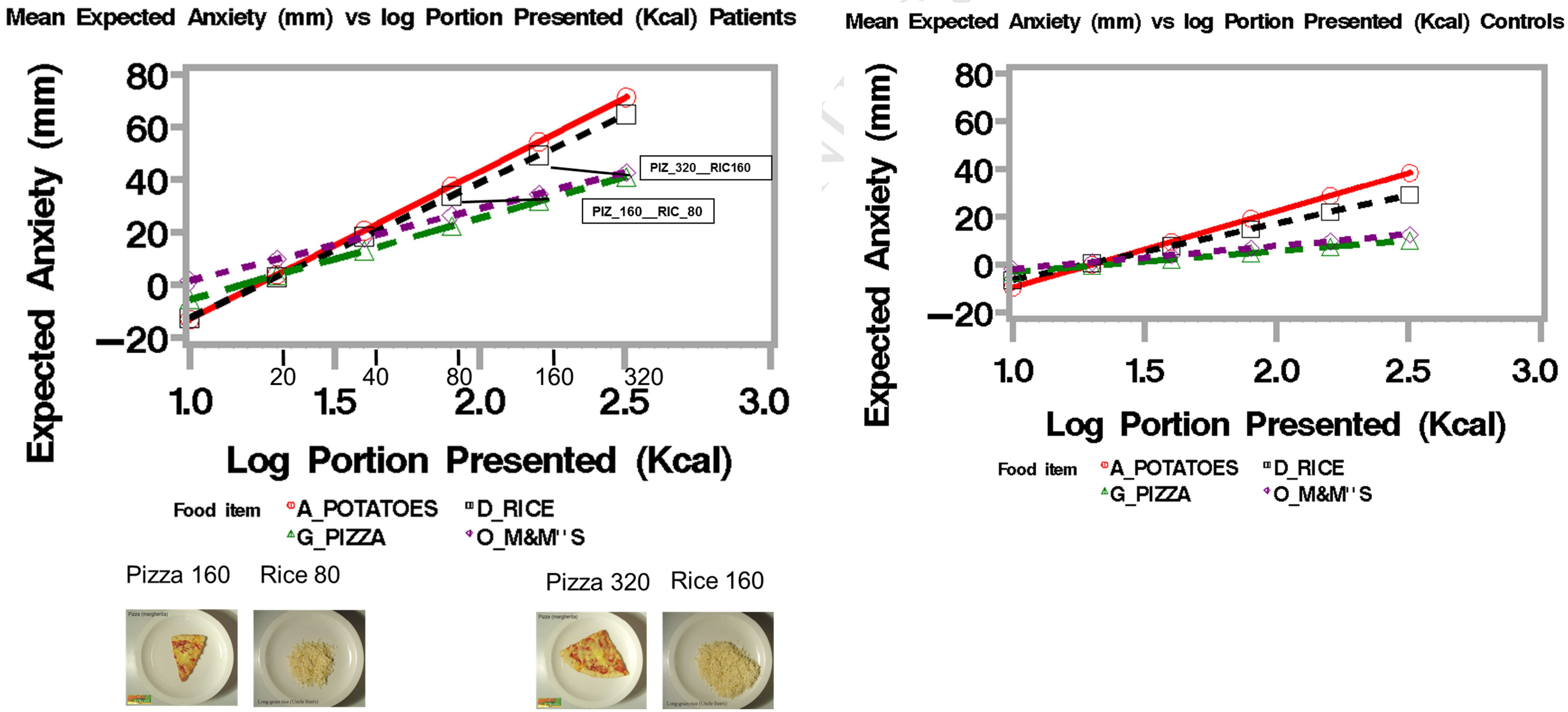

Mean Expected Anxiety (mm) vs log Portion Presented (Kcal) Patients
Expected Anxiety (mm)
80
60
40
20
0
−20
20
40
80
160
320
1.0
1.5
2.0
2.5
3.0
PIZ_320__RIC160
PIZ_160__RIC_80
Log Portion Presented (Kcal)
Food item
A_POTATOES
D_RICE
G_PIZZA
O_M&M''S
Mean Expected Anxiety (mm) vs log Portion Presented (Kcal) Controls
Pizza 160
Rice 80
Pizza 320
Rice 160

Figure 3

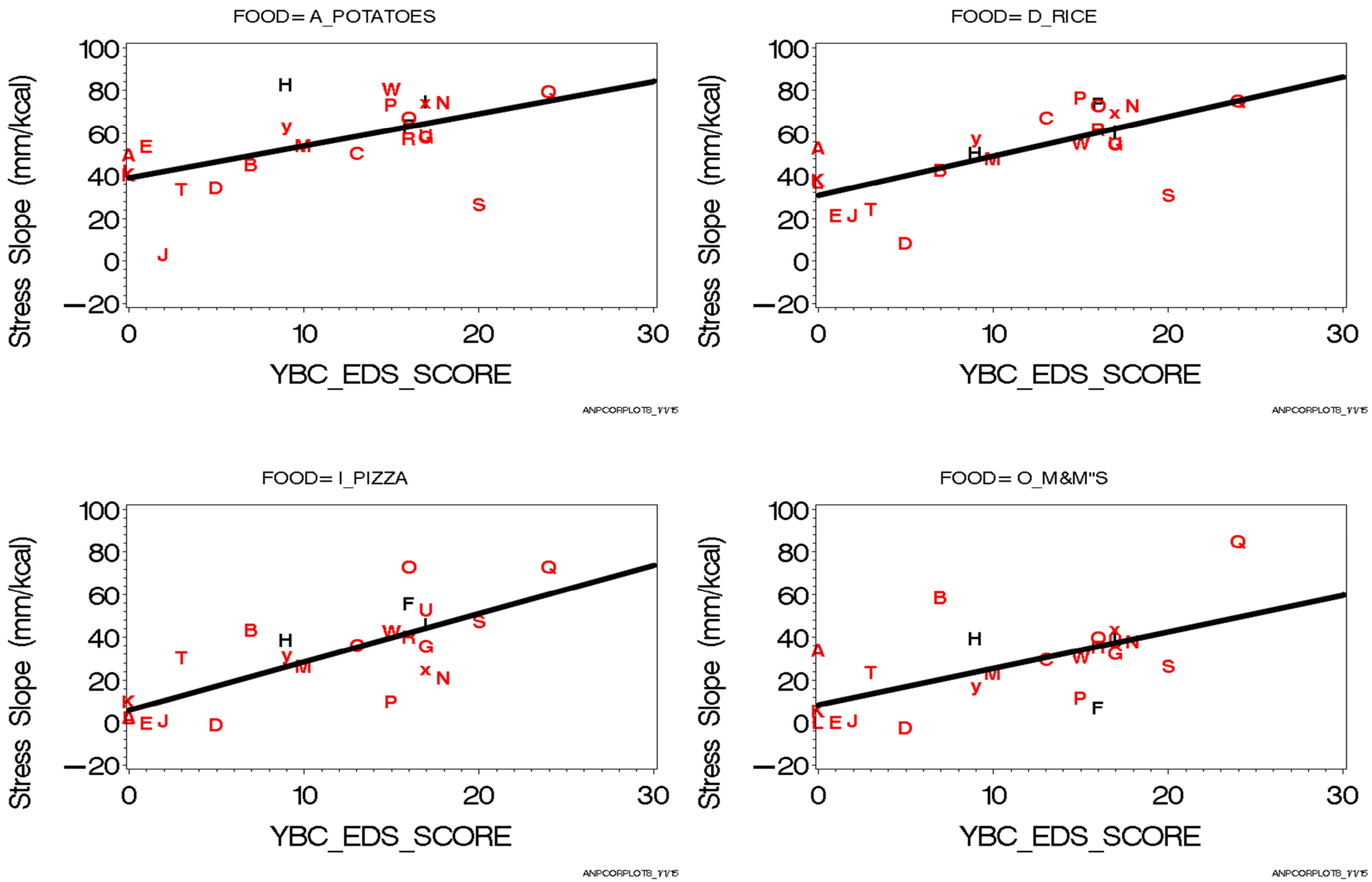
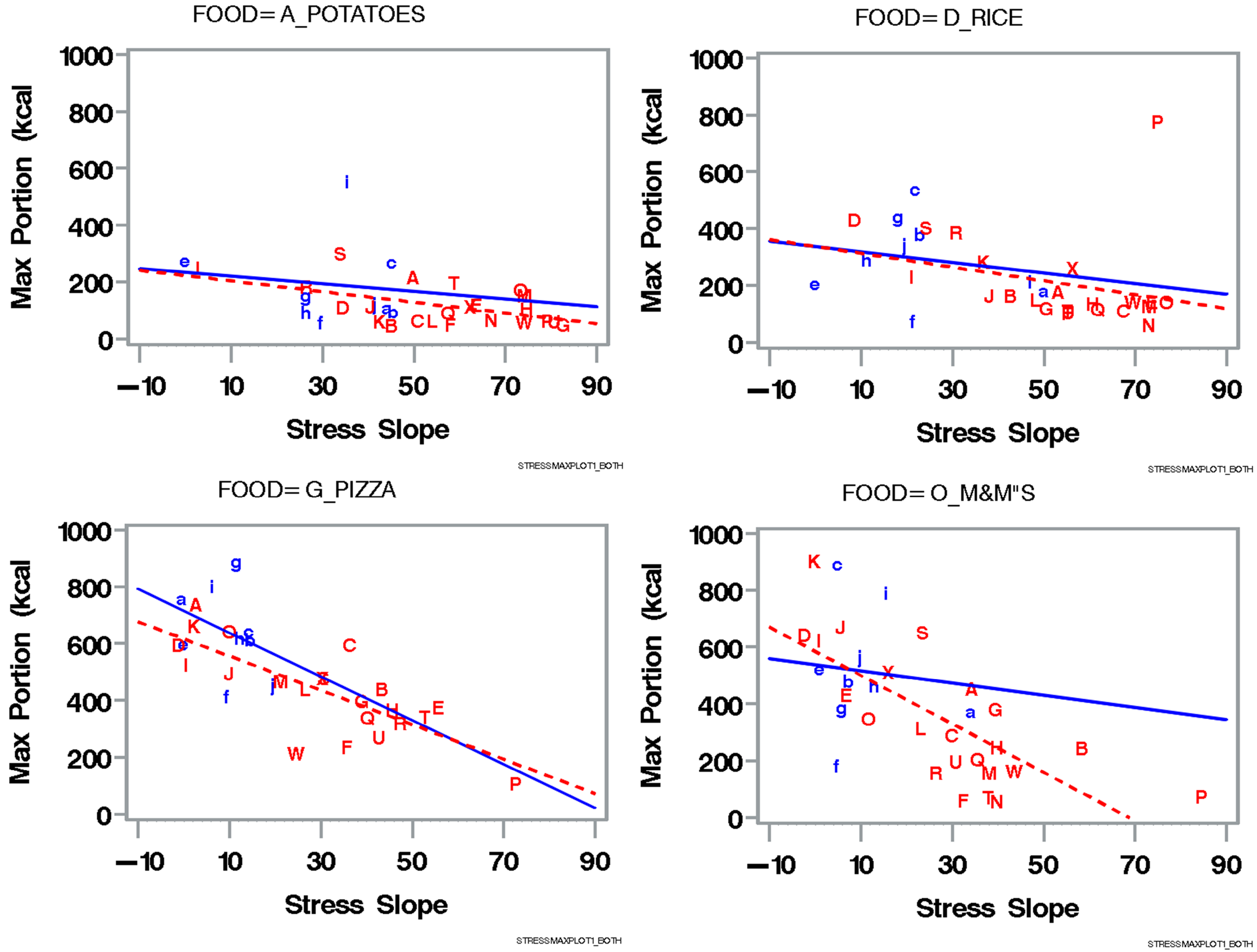

FOOD= A_POTATOES
FOOD= D_RICE
FOOD= I_PIZZA
FOOD= O_M&M"S
Stress Slope (mm/kcal)
YBC_EDS_SCORE
100
80
60
40
20
0
−20
0
10
20
30

Figure 4


FOOD= A_POTATOES
FOOD= D_RICE
FOOD= G_PIZZA
FOOD= O_M&M"S
Max Portion (kcal
Stress Slope
1000
800
600
400
200
0
−10
10
30
50
70
90
STRESSMAXPLOT1_BOTH