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Altered interoceptive awareness in anorexia nervosa: effects of meal anticipation, consumption and bodily arousal

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Abstract

Objective—Impaired interoceptive awareness (IA), the subjective perception of internal body sensations, has been proposed as a vulnerability or maintaining factor in anorexia nervosa (AN). We examined whether IA of heartbeat and breathing sensations was impaired in AN across a range of arousal levels, and whether it was influenced by meal anticipation and consumption.

Method—IA was assessed using randomized, double-blinded, bolus intravenous infusions of isoproterenol, a peripheral beta-adrenergic sympathetic agonist, and saline. Fifteen women with AN and 15 age-, and sex- matched healthy comparisons were evaluated before and after consumption of a 1000 Calorie meal. During each infusion participants rated their moment-to-moment intensity of heartbeat and breathing sensations with a dial. To measure IA we evaluated interoceptive detection thresholds, retrospective ratings of palpitation and dyspnea intensity, and interoceptive accuracy via correlations between subjective dial ratings and observed heart rate responses.

Results—Contrary to prediction the AN group was more likely to report detection of interoceptive sensations across all conditions, an effect driven by false discriminations at low

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arousal levels. Concordant with prediction, meal anticipation was associated with intensified interoceptive sensations, particularly dyspnea. There were no differences in interoceptive accuracy.

Discussion—This represents the first demonstration of interoceptive prediction errors in AN. Although IA is unimpaired at high arousal levels in AN, prediction signals are abnormal at low arousal levels, especially during meal anticipation. Altered interoceptive prediction signaling during meal anticipation could contribute to phenotypes of high anxiety in AN or alternatively, might be explained by enhanced meal associated anxiety.

Keywords

anorexia nervosa; interoceptive awareness; interoception; eating; heartbeat; respiration; arousal

Introduction

Early clinical descriptions of patients with anorexia nervosa emphasized “a failure of recognizing bodily states as a characteristic” [1]. The marked absence of hunger signals in the face of severe malnutrition [2] has contributed to the theoretical model that abnormal interoceptive awareness may be a vulnerability or maintaining factor. Beyond perception of hunger signals, interoceptive awareness (IA) in general refers to the subjective perception of sensations originating from inside of the body, and covers a diverse array including perception of cardiovascular, respiratory, colorectal and urinary sensations.

Despite broad recognition as a clinically relevant variable in anorexia nervosa (AN) [3, 4], IA has remained relatively understudied. Initial support for its disruption involved failure to detect small volumes (1 mL) of a liquid milkshake delivered directly into the stomach in 3 individuals with AN [5]. However, other studies found no physiological differences in gastric pressure or gastric contractions, in acutely underweight and weight restored states [6, 7]. Other reports of abnormal satiety perception [8, 9], decreased aversion to repeated sucrose ingestion [10], and heightened meal associated anxiety [11, 12] raise the possibility that the experience of feeding and satiety, as well as the processing of food cues, might alter interoceptive experience in AN.

Abnormal mapping of interoceptive cues in AN may result in erroneous judgments about internal bodily states [13]. Resulting mismatch between expected versus actual outcomes produces an ‘interoceptive prediction error’ that either precipitates and/or propagates abnormal consummatory behavior. For example, exposure to food or to its conditioned stimuli (images, pictures, smells) generates an aversion that is in conflict with the inherent positive reward associated with consumption of a primary reinforcer (food). This mismatch between anticipated and experienced states induces a negative affective state, thereby motivating food avoidance [14].

An emerging neuroimaging literature supports the concept of interoceptive prediction errors in AN. Weight restored individuals exhibit increased insular and cingulate cortex activation relative to healthy comparisons when viewing food images [15, 16] and when anticipating painful thermal skin stimulation [17], yet *decreased* insular activation when tasting a food stimulus [18, 19]. The exaggerated anticipatory neural response but correspondingly

dampened reaction to stimulation may represent a deficit in central integration of expected versus experienced bodily feelings. However, differences in interoceptive perception or behavior were not observed in these studies.

To date, few studies have sought to determine if cardiorespiratory IA is impaired in AN. In a heartbeat tracking task, individuals with AN were less accurate at counting their resting heartbeat compared to an age and sex matched comparison group [20]. Women recovered from bulimia nervosa demonstrated a similar finding [21]. However, the results with these tasks are potentially biased by subjects' a priori knowledge of average heart rate [22, 23], and the tasks employed are relatively insensitive to *changes* in heart rate [24, 25]. Using a heartbeat detection method, which suffers from less confounds than the tracking method, there was no evidence for differences in interoceptive accuracy under resting conditions in a larger, mixed sample of individuals with eating disorders [26]. Methodological differences aside, these studies do not address IA across the range of physiological and affective responses relevant to homeostasis, meal consumption and emotional experience.

We therefore designed a controlled experiment capable of independently eliciting a full range of physiological arousal responses in the cardiovascular and pulmonary systems in order to measure IA in AN. We selected isoproterenol, a pharmacological agent that induces rapid and transient increases in heart rate, contractility and bronchodilation via peripheral stimulation of β_1 and β_2 adrenergic receptors. This method is less invasive than analogous investigations of IA (e.g., colorectal or esophageal balloon distension), and has been tested successfully in AN [27]. Isoproterenol produces reliable dose-dependent increases in heartbeat and breathing sensations [28]. Converging evidence suggests that awareness of these sensations requires brain regions involved in visceral perception, including the insula, cingulate and somatosensory cortices [29, 30].

We hypothesized that relative to healthy comparisons, individuals with current or lifetime AN would demonstrate: (1) impaired (i.e., statistically differentiated) detection of isoproterenol induced heartbeat and breathing sensations, (2) abnormal cardiorespiratory symptom intensity during meal anticipation, and (3) impaired interoceptive accuracy. To test these hypotheses we evaluated numerous facets of IA including interoceptive detection thresholds, interoceptive symptom magnitudes and interoceptive accuracy, before and after standardized meal ingestion (see **Supplement** for construct definitions).

Methods and materials

Participants

Seventeen individuals with current or lifetime DSM 5 criteria for AN and 17 healthy comparisons (HC) were enrolled. Healthy comparisons were screened for current major psychiatric illnesses. All participants were screened for lifetime neurological, cardiac and respiratory disease. Two HC individuals were excluded due to incomplete data. Two AN individuals were excluded due to cardiac abnormalities during isoproterenol infusions (see Supplement), leaving a complete sample of 15 AN and 15 HC individuals.

To ensure that they were not in the acute starvation state, all participants with AN were required to have a minimum body mass index (BMI) ≥ 17 on the testing day. AN individuals between age 13 and 64 were recruited from university and community settings (**Supplement**). To obtain a sample representative of patients commonly treated in community settings, select comorbid diagnoses were allowed (**Supplement** and **Table 1**). Comorbid panic disorder was exclusionary, to prevent potential interference with IA [31, 32]. Selected medication classes were allowed: selective serotonin reuptake inhibitors (SSRI), selective norepinephrine reuptake inhibitors (SNRI), or nonbenzodiazepine anxiolytics, provided a stable dose for ≥ 2 months (**Supplement**).

The study was approved by the Institutional Review Board of the University of California Los Angeles. All participants provided written informed consent and received compensation for their participation.

Infusions

Participants received 3 sets of bolus intravenous isoproterenol and saline infusions on the same day. The first infusion set involved a single blinded infusion protocol with four isoproterenol doses of 0.1, 1.0, 2.0 and 4.0 micrograms (mcg). This set ensured participant familiarity with the sensations elicited by isoproterenol prior to assessing IA, and established whether baseline sensitivity to isoproterenol (chronotropic dose 25, CD25) differed between groups. CD25, the isoproterenol dose necessary to increase the participant's heart rate by 25 beats per minute above baseline, is a common measure of peripheral beta adrenergic receptor sensitivity [33, 34] known to vary in underweight AN [27].

The second infusion set occurred immediately prior to a 1000 Calorie meal. The third infusion set occurred immediately after the meal. During these sets participants rated the experience of internal body sensations, both during and immediately following multiple bolus infusions. Participants received 14 bolus infusions in each set: 7 isoproterenol (0.1, 0.25, 0.5, 0.75, 1, 2, 4 micrograms), and 7 saline. Additional lower doses were included in these sets to improve detection of deviations in IA from baseline. Infusion administration was randomized and double blinded (for additional details see **Figure S1** and **Supplemental Methods**.)

Tasks

To index IA, concurrent dial ratings and retrospective symptom ratings were recorded, similar to previous accounts [28, 30]. During each infusion period participants were instructed to “pay attention to the sensations and emotions you experience” while breathing normally, with the eyes open, and without taking their pulse. They were instructed to rotate a dial to “accurately rate the ongoing, moment-to-moment experience of the overall intensity of your heartbeat and breathing sensations.” The dial ranged from 0 (“normal, i.e., no change in intensity”) to 10 (“most ever”). The dial was set to zero at the beginning of each infusion, and participants were specifically instructed to “only turn the dial above zero if you notice an increase in the intensity of your heartbeat and breathing sensations due to what you received in the infusion.” Immediately after each infusion, participants retrospectively rated heartbeat and breathing sensation intensity, and their affective responses.

Meal manipulation

Participants fasted overnight. Upon arrival they received a 300 Calorie breakfast. Infusions began 90 minutes afterwards. To maximize food-related emotional arousal, immediately prior to the second infusion set participants were reminded they would break for a 1000 Calorie lunch directly afterwards, and that they were required to consume the full meal. The third infusion set started immediately after lunch (**Figure S2** and **Supplemental Methods.**)

Apparatus

Physiological data including heart rate, respiratory rate and skin conductance were recorded continuously during all infusions with an MP150 acquisition unit (Biopac Systems, Inc, Goleta, CA). (**Supplemental Methods.**)

Interoceptive measures

To assess interoceptive detection (I_D), participants' dial ratings were dichotomized using a custom matlab script (**Supplement**).

To assess interoceptive symptom magnitude (I_M), dial ratings were summated across each infusion, approximating the integral or area under the curve (AUC) yielding a concurrent measure of cardiorespiratory intensity. To evaluate organ-specific I_M , retrospective baseline adjusted ratings of palpitation and dyspnea intensity were measured (as in [28]).

To assess interoceptive accuracy (I_{Acc}), cross correlations for each dose were calculated from mean-centered dial ratings and mean-centered instantaneous heart rate changes occurring during each two-minute infusion interval (as in [28]) (see Supplement for additional cross correlation measure details.) (For interoceptive construct definitions see **Supplement.**)

Statistical analysis

Demographic data were analyzed via independent samples t tests, and categorical variables via chi-squared tests. Continuous data were analyzed using linear mixed effects models with repeated measures, with group, meal (pre, post) and dose as fixed effects and individual subjects as random effects. Dial detection rates were analyzed using a mixed effects logistic regression model, with group, meal (pre, post) and dose (low, high) as fixed effects and individual subjects as random effects. P values $\leq .05$ were considered statistically significant, except when Bonferroni corrections for multiple comparison were applied (see **Supplemental Methods** for model selection and Bonferroni adjustment details.)

Results

Demographic characteristics

As expected, the AN group demonstrated a lower BMI ($t_{28} = -3.27$, $p = .022$), and expressed higher anxiety ($t_{28} = 4.63$, $p = .0002$), and depression ($t_{28} = 5.42$, $p = .0001$) than healthy comparisons (**Table 1**). Eating disorder severity was in the moderate range (average EDE global score = 2.8; SD = 1.4). The groups did not differ in age, sex, or education, and there were no differences in peripheral adrenergic sensitivity as measured by CD25 (**Table 1**). By

design, the groups consumed an equivalent number of Calories, and no differences in fasting or post-prandial glucose levels were observed (**Table S1**). Eight individuals had one or more secondary comorbid disorders. No differences in IA or isoproterenol response were observed for individuals with comorbid diagnoses (**Supplemental Results**). Four AN individuals were taking medication (SSRI $n = 3$, SNRI $n = 1$). Given the small sample size of this subgroup no additional comparisons were made.

Physiological changes

Isoproterenol resulted in significant dose related increases in heart rate ($F(1, 6) = 104.94$, $p < .0001$) (**Figure S3, S4 and S5**), respiratory rate ($F(1, 6) = 4.89$, $p = .001$) and skin conductance amplitude ($F(1, 6) = 5.50$, $p = .005$) (**Figure S6**). However, there were no group differences in response (heart rate: $F(1, 28) = .01$, $p = .94$; respiratory rate: $F(1, 28) = .04$, $p = .85$; skin conductance: $F(1, 28) = .30$, $p = .59$) or group by meal differences across all measures (heart rate: $F(1, 1) = .06$, $p = .81$; respiratory rate: $F(1, 1) = .51$, $p = .48$; skin conductance: $F(1, 1) = .80$, $p = .38$), indicating the groups exhibited similar responses to isoproterenol stimulation. There was a significant effect of meal on heart rate ($F(1, 1) = 10.20$, $p = .003$) indicating lower post meal heart rate responses, but there was no effect on respiratory rate ($F(1, 1) = .00$, $p = .95$) or skin conductance ($F(1, 1) = 1.03$, $p = .32$).

Interoceptive awareness results

Hypothesis 1: interoceptive detection

There was a significant group difference in dial detection ($F(1, 804) = 4.80$, $p = .029$) but in the opposite direction than predicted, with the AN group four times more likely to endorse detection of increased interoceptive sensation across all conditions (Odds Ratio (OR): 4.04, 95% Confidence Interval (CI): 1.16, 14.08) (**Figure 1**). Closer inspection of the detection data revealed a potential discrepancy in detection rates at low arousal levels (saline, 0.1, 0.25 mcg) vs. high arousal levels (0.5 mcg and above), with the AN group appearing more likely to endorse increased interoceptive sensations at low levels of arousal. Due to the non-predicted direction of this finding, we conducted an exploratory *post hoc* analysis comparing lower vs. higher arousal levels for group differences. At low arousal levels, the AN group was significantly more likely to report increased interoceptive sensation during the pre-meal (OR: 4.46, 95% CI: 1.26, 15.84, $p = .021$), but not the post-meal state (OR: 3.02, 95% CI: 0.84, 10.81, $p = .09$). At high arousal levels, there were no significant pre-meal (OR: 6.96, 95% CI: 0.85, 56.79, $p = .07$) or post-meal differences (OR: 2.77, 95% CI: 0.48, 15.93, $p = .25$) (**Table S2, Supplement**). Given that some interoceptive stimulation occurs even at low isoproterenol doses, we restricted a subsequent analysis to only the saline infusions. The AN group demonstrated higher average detection rates during saline infusions than HCs before the meal ($t_{28} = 2.47$, $p = .022$) but not afterwards ($t_{28} = 1.68$, $p = .10$).

Hypothesis 2: interoceptive meal anticipation

There were significant group by meal interactions for overall cardiorespiratory magnitude (dial AUC; $F(1, 801) = 7.62$, $p = .0059$) and dyspnea ($F(1, 801) = 6.52$, $p = .011$), indicating that the AN group endorsed greater pre meal intensity of cardiorespiratory sensations and greater pre meal dyspnea than the HC group (**Table 2, Figure 3**). The interaction for

palpitations was not significant after bonferroni correction ($F(1, 801) = 4.56, p = .033$) (Table 2, Figure 3). There was no effect of meal on palpitation ($F(1, 801) = 1.54, p = .21$), dyspnea ($F(1, 801) = 0.15, p = .70$) or dial AUC ratings ($F(1, 801) = 2.71, p = .10$). There was a main effect of group on dyspnea ratings, with the AN group endorsing greater dyspnea intensity ($F(1, 801) = 7.56, p = .0061$). There were no other significant group effects.

Hypothesis 3: interoceptive accuracy

Contrary to predictions there were no significant group differences in the zero cross correlation ($F(1, 801) = 2.96, p = .09$) or in the maximum cross correlation ($F(1, 801) = 1.04, p = .31$) (Figure 4, Table 2), nor were there group by meal interactions for the zero cross correlation ($F(1, 801) = 3.57, p = .06$) or maximum cross correlation ($F(1, 801) = 3.10, p = 0.08$). There were, however, significant effects of meal on the zero cross correlation ($F(1, 801) = 4.71, p = .03$) and maximum cross correlation ($F(1, 801) = 16.94, p < .0001$), with lower accuracy following meal ingestion. A secondary, *post hoc* analysis of within group meal differences (pre vs. post) revealed significant differences in zero and maximum cross correlation values for the AN but not HC group (Table S3, Supplement), indicating that meal consumption decreased interoceptive accuracy principally in the AN sample. As expected, there were significant dose effects for the zero cross correlation ($F(7, 801) = 255.85, p < .0001$), maximum cross correlation ($F(7, 801) = 364.00, p < .0001$) and lag time ($F(7, 801) = 10.38, p < .0001$). There were no significant differences in lag time for group ($F(1, 801) = 1.36, p = .24$), meal ($F(1, 801) = 0.01, p = .91$) or group by meal interaction ($F(1, 801) = 0.34, p = .56$).

Discussion

This study represents the first demonstration of interoceptive prediction errors in AN. Individuals with AN had difficulty detecting and separating actual interoceptive sensations from anticipated ones, particularly at low levels of bodily arousal, compared with healthy controls. As arousal increased, both groups displayed appropriate and equivalent increases in interoceptive accuracy. Moreover, individuals with AN experienced abnormally intense cardiorespiratory sensations, particularly of the breath, and especially as meal consumption was approaching.

Contrary to our first hypothesis, we did not find lower rates of detection for isoproterenol induced interoceptive changes. Instead, the AN group was significantly more likely to endorse interoceptive changes, across all conditions. A *post hoc* analysis did not find group differences in detection rates at high doses, which we have previously shown have a high probability of detection [28, 30]. Individuals with AN were more likely to incorrectly endorse interoceptive changes at low doses (with a low probability of detection) and during saline infusions. These findings are consistent with prior reports [21][35] in the sense that the AN and bulimia nervosa groups had imprecise estimations of heart rate during conditions of low arousal.

Potential sources of false perceptions at low arousal levels in AN warrant consideration. Individuals with AN may have a general aversion towards visceral sensations, which could manifest as an increased detection bias. Aversion of visceral sensation could be triggered by

food stimuli or during pre meal states, thereby increasing the expectation for and reporting of interoceptive change. Alternatively, pre meal states could preferentially increase anxiety in AN irrespective of visceral aversion, lead to amplification of anticipatory signals, and lead to an increased tendency to endorse visceral experiences. In both respects, the current findings are in accord with the concept of altered interoceptive prediction signaling, as previously hypothesized by Paulus and Stein [36] and Kaye et al [13, 14]. Differentiating the relative contributions of anxiety from visceral sensation aversion will require further studies.

Consistent with our second hypothesis, we found that the AN group experienced cardiorespiratory sensations with increased intensity during meal anticipation, indicating that certain aspects of interoceptive representation (specifically, I_M) are subject to influence by the external environment. Food may be an anxiogenic stimulus in AN, as these interoceptive sensations were particularly enhanced prior to, but not following, meal receipt. Dyspnea ratings were also higher in the AN group independently of meal state, raising the possibility that respiratory interoceptive sensitivity might represent an intermediate phenotype that supports or mediates the physiology in AN. As no studies to date have directly examined respiratory interoceptive sensitivity in anorexia nervosa, independent confirmation is needed.

We did not find evidence to support our third hypothesis that interoceptive accuracy would be impaired in AN. This finding is consistent with a recent study [26] finding no group differences in I_{Acc} via a heartbeat detection task. The authors posited that the lack of differences may have been due to the high degree of task difficulty, task fatigue, and assessment of I_{Acc} during resting states when heartbeat sensations are not typically reported. Such reports are consistent with our previous experience [22], which subsequently led us to develop [28] and utilize the current approach. We did find that meal ingestion significantly impacted I_{Acc} , with lower accuracy following meal ingestion. Since both groups displayed lower heart rate responses in the post meal state, development of tolerance to the pharmacological effects of isoproterenol might explain the lowered post meal accuracy. However, a secondary analysis revealed that the lower post meal cross correlations were driven predominantly by decreases within the AN group, suggesting that the effects of meal consumption might preferentially lower I_{Acc} in AN. Contributing factors might include reduced post meal interoceptive intensity, attenuated anxiety in the post meal state, or differential effects of the food stimulus on digestive and neuroendocrine systems in AN. It appears unlikely that baseline I_{Acc} represents a specific phenotype of anorexia nervosa. Instead, meal consumption and peri-meal time periods seem to signify relevant behavioral targets capable of altering interoceptive experience in AN.

Limitations

Several issues warrant consideration: (1) this study employed a small sample size. (2) While AN was the primary clinical diagnosis, comorbid diagnoses were present in a number of the individuals. (3) Generalizability to other channels of IA (e.g., gastrointestinal, urinary), and proprioceptive or exteroceptive sensitivity is unclear. This is relevant, as other disrupted somatosensory experiences have been reported in AN [37-39]. (4) Elevated trait levels of anxiety and depression in the AN group could have contributed to the current findings.

Conflicting findings of anxiety [31, 32, 40], and depression [41, 42] on I_{Acc} highlight an additional need to understand their precise contributions to interoceptive experience in AN. (5) Studying current and previously ill AN individuals, and individuals in varying forms of treatment limits the ability to draw conclusions about the acutely ill, underweight phase of the illness. Accordingly, the observed differences are indicative of trait phenomena persisting beyond the acute starvation state. (6) SSRI/SNRI treatment in a minority of the sample could have affected the current results. However, these medications may only have a limited impact on interoceptive cue discrimination [43].

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Interoceptive detection rates during bolus isoproterenol infusions, before and after consumption of a 1000 Calorie meal

The AN group demonstrated abnormal detection at low arousal levels, as evidenced by increased detection rates at the saline, 0.1 and 0.25 mcg doses (* $p < .05$). AN = anorexia nervosa. HC = healthy comparison.

Figure 2. Interoceptive symptom magnitude during bolus isoproterenol infusions, before and after consumption of a 1000 Calorie meal

Participants concurrently rated the overall intensity of heartbeat and breathing sensations by rotating a dial during infusions. Ratings were measured by summing the area under the curve (AUC) of dial ratings generated during each infusion. Participants also provided retrospective ratings of dyspnea and palpitation symptom intensity after each infusion. A. Pre meal and post meal cardiorespiratory intensity. A significant group $\times$ meal interaction was observed ($**p < .01$; see table 2). B. Pre meal and post meal dyspnea intensity. A significant group $\times$ meal interaction was observed ($*p < .05$) as well as a significant group effect ($###p < .01$; see table 2). C. Pre and post meal palpitation intensity. Figures represent group means. Error bars are SE. Axis markers for the 0.1, 0.25 and 0.75 mcg doses have been omitted to improve figure clarity. AN = anorexia nervosa. HC = healthy comparison.

Figure 3. Interoceptive accuracy during bolus isoproterenol infusions, before and after consumption of a 1000 Calorie meal

A. Pre meal and post meal zero order cross correlation between interoceptive dial rating and heart rate response. B. Pre and post meal maximum cross correlation between interoceptive dial rating and heart rate response. There were no significant between group differences in these measures, but there was a significant effect of meal on both zero and maximum cross correlation (* $p < .05$, ** $p < .01$; see table 2). Figures represent group means. Error bars are SE. Axis markers for the 0.1, 0.25 and 0.75 mcg doses have been omitted to improve figure clarity. AN = anorexia nervosa. HC = healthy comparison.

Table 1

Demographic characteristics.

	Anorexia Nervosa (AN)	Healthy Comparison (HC)	t-Test	p
Age (years)	23.0+/- 3.8	22.3 +/- 4.5	-0.48	.63
Sex	15 Females	15 Females		
Body Mass Index (BMI)	19.2 +/- 1.6	22.7 +/- 3.7	3.27	.004
Ethnicity (% Caucasian)	60	40		
Education (years)	14.7 +/- 2.5	14 +/- 2.2	-0.87	.39
Beck Depression Inventory	12.1 +/- 6.9 **	2.1 +/- 2.1	-5.42	< .001
Beck Anxiety Inventory	13.8 +/- 8.3 **	3.1 +/- 3.2	-4.63	< .001
Eating Disorder Examination – global score	2.8 +/- 1.4	–		
AN restricting subtype (%)	73.3	–		
Age of onset (years)	16 +/- 2.4	–		
Illness duration (years)	6.8 +/- 4.1	–		
Largest weight loss (lbs)	27.9 +/- 10.2	–		
Lowest BMI	15.3 +/- 1.7			
Comorbid diagnoses (%)				
Any	53	–		
GAD	27	–		
MDD	13	–		
OCD	13	–		
>2 comorbid disorders	13	–		
Psychotropic medication (%)	27			
Baseline heart rate (bpm)	70.1 +/- 12.4	70.5 +/- 9.3	0.10	.92
CD25 – baseline	5.2 +/- 4.6	4.0 +/- 1.3	-0.99	.34
CD25 – pre meal	5.30 +/- 2.6	5.3 +/- 2.6	-0.04	.97
CD25 – post meal	7.1 +/- 4.3	6.2 +/- 3.1	-0.66	.52

Means +/- standard deviation. CD25: Chronotropic Dose 25, isoproterenol dose in micrograms (mcg) required to increase the heart rate by 25 beats per minute (bpm).

* p < .05

** p < .001. GAD: generalized anxiety disorder. MDD: major depressive disorder. OCD: obsessive compulsive disorder.

Table 2

Tests for fixed effects for the continuous interoceptive outcome measures.

Effect	Zero Cross-Correlation	Maximum Cross-Correlation	Absolute Lag Time	Palpitations	Dyspnea	Dial AUC
Dose	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
Group	0.09	0.31	0.24	0.26	0.0061	0.17
Meal	0.030	<0.0001	0.91	0.21	0.70	0.10
Group × Meal	0.06	0.08	0.56	0.033	0.011	0.0059

All numbers are p values. The interaction comparison controlled for dose effects.