Study Title:
Fear, Gastrointestinal Distress, and Interoception: Physiological and Psychological Mechanisms in Eating Disorders

NCT ID: Not Yet Assigned

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Objective

Although more than 28 million Americans will be affected by an eating disorder in their lifetime, even the best interventions fail to achieve symptom remission in most patients.[1,2] Empirically-supported meal-related interventions often suffer from poor adherence due to postprandial gastrointestinal (GI) distress (e.g., nausea, stomachache),[3–6] making GI distress arguably a primary barrier to improved treatment outcomes.[7–9] The proposed study seeks to test the first causal model of GI distress in eating disorder maintenance.

Fear of food, eating and weight gain[10,11] are hypothesized to contribute to GI distress through two direct mechanisms: 1) enhanced short-term gut peptide response [cholecystokinin (CCK) and peptide YY (PYY)][12,13] and 2) increased subjective fullness due to biased interoception.[14] In this novel model, each of these mechanisms directly contribute to GI distress, and they also interact such that fear indirectly increases fullness via enhanced CCK and PYY response. In turn, greater postprandial distress promotes increased urges for restrictive eating behaviors. Restrictive eating behaviors, including fasting and reduced meal size, are problematic behaviors across eating disorders, regardless of weight status, and are central to current conceptualizations of eating disorder maintenance.[15,16]

Aim 1: Test fear as a contributor to GI distress within individuals with eating disorders.

H1a: Relative to the low fat test meal, the high fat test meal will increase subjective ratings of fear and skin conductance levels.

H1b: Relative to the low fat test meal, the high fat test meal will increase GI distress.

Aim 2: Test peptide response and subjective fullness as mediators of fears effects on GI distress.

H2a: Relative to the low fat test meal, the high fat test meal will increase CCK and PYY response.

H2b: Relative to the low fat test meal, the high fat test meal will increase subjective ratings of fullness.

H2c: Increases in peptide response and subjective fullness will each mediate the relationship between fear and GI distress.

Exploratory Analysis: A serial multiple mediation model will examine fear as a cause of CCK and PYY increases and in turn, increases in fullness, GI distress, and urges to restrict food intake.

Design

Women with eating disorders who experience gastrointestinal distress will be recruited to participate in a three-part study. At Study Visit 1, participants will provide informed consent and complete interviews, have height and weight taken, and complete a questionnaire battery to confirm eligibility. After confirming eligibility, participants will be randomized to test meal order. Following an overnight fast, participants will complete Study Visit 2 and 3 on two separate mornings, at least 48 hours apart, at the Ohio University Clinical and Translational Research Unit (CTRU). At Study Visits 2 and 3, participants will eat a test meal and complete assessments pre- and postprandially. These assessments include skin conductance, subjective reports of fullness, gastrointestinal distress, and urges to engage in restrictive eating behaviors, and blood draws. Order of exposure to high fat and low fat test meal instructions will be

randomized across the sample in a cross-over design. In both instances, participants will be provided the same food. To support the planned deception, the study will be advertised as Taste, Psychological, and Physiological Responses to Food Intake Associated with Disordered Eating. The description of the test meal must be manipulated to activate fear of food, eating, and weight gain while holding the nutrient content of the meal constant in order to compare the psychological and physiological responses unique to fear. A high fat, rather than low fat, yogurt is needed to maximize peptide and fullness responses.

Methods

Recruitment: Women will be recruited from the Athens, Ohio, area to participate in a study assessing the taste and physiological response to food associated with disordered eating (Taste, Psychological, and Physiological Responses to Food Intake Associated with Disordered Eating.). Participants will be recruited via the following methods: 1) e-mails to enrolled undergraduate and graduate students as well as faculty and staff at Ohio University; 2) flyers and 3) e-mails to women ages 18 to 40 who reside within 75 miles of Athens, Ohio, via researchmatch.org. E-mails and advertisements will have links to an online eligibility screen via REDCap that will include a brief description of the study and a brief questionnaire battery to assess the following inclusion and exclusion criteria. They will also be screened for study 19-F-33, and will be invited to participate in 19-F-33 if they are ineligible for the current study.

Phone Screen: Women who appear eligible based on online screening information will complete a phone screen with a member of the research team to confirm likely eligibility. Participants will be informed that the purpose of the study is to assess the taste perceptions of, and biological and psychological responses to, high and low fat food, and that, if eligible, they will be randomized to eat either two low fat yogurts, two high fat yogurts, or one high fat and one low fat yogurt. Consent forms for "Body Image and Taste Concerns" 19-F-33 will be reviewed to ensure the participant has not already participated in the paradigm before contacting potential participants via phone.

Study Visit 1: Likely eligible women will complete a three-hour eligibility confirmation appointment in Dr. Forney's lab in Porter Hall or at CTRU. Trained graduate students or Dr. Forney will obtain informed consent. During the consent process, participants will be informed that, if eligible, they will be randomly assigned to participate in one of three conditions: eating two high fat yogurts, eating two low fat yogurts, or eating one high fat and one low fat yogurt. In this way, participants will be providing consent to eat two high fat yogurts. Graduate students or Dr. Forney will administer semi-structured diagnostic interviews to confirm eligibility. The Structured Clinical Interview for DSM-5 assesses current and lifetime suicidality. Dr. Forney, Dr. Austin, or Dr. France, licensed psychologists, will be available in the case of elevated suicidality or any other psychiatric emergency. In the event that a participant endorses current suicidal ideation, intent or plans, the graduate interviewer will conduct a suicide risk assessment and help the participant develop a safety plan; the graduate interviewer will consult with Dr. Forney or a back-up psychologist (Dr. Austin or Dr. France, as scheduled) before the participant leaves. All participants will be provided with mental health resources. Participants will have height and weight measured and complete a questionnaire battery. Following completion of assessments, and if eligible, the graduate student or Dr. Forney will draw an envelope from the next in a series of sequential, numbered, opaque sealed envelopes to inform the participant about randomization condition (i.e., high fat-low fat or low fat-high fat). All participants will be told that they are randomized to either the "high fat low fat" condition or the "low fat high fat" condition.

Study Visits 2 and 3: For the Study Visits 2 and 3, the same procedures will occur. Briefly, participants will arrive between 7:30 am and 9 am at the CTRU, have an indwelling venous catheter inserted by a research nurse, and have sensors attached on the distal phalanges of the index and middle finger of their non-dominant hand. The sensors will record electrodermal responses (skin conductance) using a Biopac system. The participant will complete repeated blood draws and visual analogue rating scale ratings before and after consuming a test meal. More detailed information about these procedures are below in the section labelled "Study Protocol- Study Visit 2 and 3." Participants will be asked to refrain from eating or drinking anything other than water from 10 pm the night before. Participants will be asked to abstain from taking any medications other than hormonal contraceptives and/or a prescribed SSRI three days before their study visit. Study Visits 2 and 3 will be scheduled during the follicular phase (within 10 days of menses onset) for women who are naturally ovulating. Women taking hormonal contraception will be scheduled based on their convenience.

The description of the test meal will be randomly assigned across study visits 2 and 3. In the neutral condition, participants will be instructed to eat a low-fat yogurt (approximately 8% fat). In the fear condition, participants will be instructed to consume a full-fat yogurt (approximately 60% fat). In both conditions, participants will eat the same yogurt consisting of 170g of the Greek Goods Strawberry with Honey Yogurt and 45g of Heavy Cream (60% fat). By keeping the same meal, we will be able to evaluate changes in anxiety, fullness, and GI distress that are due to the fear manipulation alone. Using a high fat meal is needed to maximize the release of the relevant gut hormones (e.g., CCK, PYY).

Each visit will take approximately 2.5 hours to complete and participants will be compensated $63 for each study visit. Following the completion of both study visits, participants will be asked to describe study aims (manipulation check) and debriefed about the test meal composition and study aims.

Blood Draw Visit Study Protocol

Day before: participants will be reminded to refrain from eating or drinking anything other than water after 10 pm the evening before.

Approx. 30 minutes before test meal: Participant arrives; is re-oriented to purpose of today's visit. Research nurse will take temperature, blood pressure and pulse, and will ensure participant is feeling well. The participant will be rescheduled if ill. Start time can be as late as 9 am, with 7:30 am preferred.

Approx. 20 minutes before test meal: Research nurse inserts indwelling venuous catheter in the non-dominant arm, consistent with SOP 605.00; approximately 5 minutes later, research staff attaches electrodermal sensors to the index and middle finger of non-dominant hand; participant then has acclimation period and completes a questionnaire about recent eating disorder symptoms

Approx. 10 minutes before test meal: A research assistant will administer VAS.

Test meal: A research assistant will provide the participant information about the nutrient content of the test meal (i.e., high fat or low fat; the test meal order will be randomly assigned). The research nurse will draw blood (up to 5 mL), discarding the first mL and drawing up to 4 mL into EDTA- prepared (lavender top) tube(s). A member of research staff will gently invert the

lavender tubes several times immediately after blood collection. A member of research staff will administer a VAS. After the completion of the VAS packet, the participant will consume a yogurt test meal over a 10-minute period. A member of research staff will instruct the participant to eat the yogurt, sharing the fat content based upon which condition the participant was randomly assigned (i.e., high fat or low fat instructions).

Approx. 10 minutes after test meal: Approx. 10 minutes after being given the test meal content, the research nurse will draw up to 5 mL of blood using the same procedure. A member of research staff will process the blood sample as described above, while a second member of research staff administers a taste perception assessment and VAS.

Approx. 20 minutes after test meal: The research nurse will draw up to 5 mL of blood using the same procedure. A member of research staff will process the blood sample as described above, while a second member of research staff administers the VAS.

Approx. 30 minutes after test meal: The research nurse will draw up to 5 mL of blood using the same procedure. A member of research staff will process the blood sample as described above, while a second member of research staff administers the VAS. Following completion of this time point, a member of research staff will remove the electrodermal sensors.

Approx. 60 minutes after test meal: The research nurse will draw up to 5 mL of blood using the same procedure. A member of research staff will process the blood sample as described above, while a second member of research staff administers the VAS.

Approx. 90 minutes after test meal: The research nurse will draw up to 5 mL of blood using the same procedure. A member of research staff will process the blood sample as described above, while a second member of research staff administers the VAS. The research nurse will then remove the IV consistent with protocol 605.00. The participant will be free to leave.

Yogurt preparation: All food ingredients will be stored in a refrigerator used only for food in either Dr. Forney's lab or the CTRU. All materials (i.e., bowls, spoons, stick blender, etc) will be washed in hot water and kept clean using household dish detergent (e.g., Palmolive). Research team members will wash their hands using hot water and soap prior to preparing the yogurt. They will use utensils (e.g., spoons, spatulas) to measure out the yogurt ingredients into a clean bowl and blend the ingredients using a spoon. Yogurts will be prepared the morning of the study visit and stored in a clean bowl in a refrigerator either in Dr. Forney's lab or the CTRU. Following the study visit, a research team member will wash utensils in hot water with household dish detergent (e.g., Palmolive). A member of the research team will measure the food portion using a scale and ensure food is used prior to its expiration date.

Participants will receive reminders before their study visits through their preferred means of communication (e.g., email, text message, or phone call).

Blood samples will be processed as described in the Study Protocol and frozen at -80 C until assayed for hormones.

In the event that there is difficulty collecting blood samples with the IV, the participant will be offered to finish the study visit using single venipunctures.

Statistical Analysis Plan

We will enroll 152 subjects at Study Visit 1. Based on a prior study using similar screening procedures and multi-visit study design (R01MH111263), we conservatively anticipate 25% attrition after Study Visit 1 and 15% attrition after Study Visit 2. This will allow 97 participants to complete study Visit 3 and appropriately power Hypotheses 1a, 1b, 2a, 2b, and 2c (≥ 80% power). Our exploratory serial multiple mediation model will be underpowered but will generate effect sizes for future research.

Aim 1: Test fear as a contributor to GI distress within individuals with eating disorders.

H1a: Relative to the "low fat" test meal, the "high fat" test meal will increase subjective ratings of fear and skin conductance levels.

Analytic Plan: Difference scores will be computed for both test meals by comparing mean skin conductance level (expressed in log units) over the 10 minute meal period compared to the 10 minute period before the meal. Area under the curve with respect to increase (AUCi) will be used to characterize changes in subjective ratings for fear from the 10 minutes period prior to the meal until immediately after the meal. Two paired subjects t-tests will compare responses in the "high fat" instruction to responses in the "low fat" instruction. Peak skin conductance levels will also be investigated as an indicator of fear in sensitivity analyses.

Power Analysis: Using progressive muscle relaxation prior to a meal, prior research has observed a medium decrease in anxiety in a treatment-seeking eating disorder sample (within-subject d estimate range .56 to .97 assuming correlations between time points ranging from .4 to .8).[17] Therefore, we anticipate that the test meal manipulation will cause a change in fear that is of at least medium effect size. Using an alpha of .025 to account for multiple measures of fear (self-report and skin conductance levels) and achieving 80% power, a sample of 41 women will be needed to detect at least a medium effect size.

H1b: Relative to the "low fat" test meal, the "high fat" test meal will increase GI distress.

Analytic Plan: AUC_i over the 10 minute period immediately before the meal until the end of the test meal will be calculated for subjective ratings of GI distress. A paired subjects t-tests will compare responses in the "high fat" instruction to responses in the "low fat" instruction.

Power Analysis: Our preliminary data support a moderate association between fear and GI distress; a sample of 34 women will be needed to detect a medium effect size in GI distress with an alpha of .05 and achieving 80% power.

Aim 2: Test peptide response and subjective fullness as mediators of fear's effects on GI distress.

H2a: Relative to the "low fat" test meal, the "high fat" test meal will increase CCK and PYY response.

Analytic Plan: AUC_i will be calculated from immediately before the meal to 90 minutes after the meal to assess CCK and PYY response. Two paired subjects t-tests will compare CCK and PYY responses in the "high fat" instruction to responses in the "low fat" instruction. Power Analysis: In a study of rats, the acute restraint task was associated with a ~33% increase in CCK immunoreactivity relative to no stress.[12] Similarly, a stress task was associated with a large increase in PYY in women with anorexia nervosa (d=.93) relative to healthy controls. Therefore, we conservatively anticipate that the test meal manipulation will cause a change in CCK and PYY that is of a medium effect size (d=.5). Using an alpha of .025 to account for multiple comparisons and achieving 80% power, a sample of 41 women will be needed.

H2b: *Relative to the "low fat" test meal, the "high fat" test meal will increase subjective ratings of fullness.*
Analytic Plan: AUC_i will be calculated from immediately before the meal to 90 minutes after the meal to assess subjective fullness. A paired subjects t-test will compare fullness responses in the "high fat" instruction to responses in the "low fat" instruction.
Power Analysis: Using progressive muscle relaxation prior to a meal, prior research observed a medium effect size change in self-reported fullness (within subject d estimate range .40 to .69 assuming correlations between time points ranging from .4 to .8).[17] Therefore, we anticipate that the test meal manipulation will cause a change in fullness that is of at least medium effect size. Using an alpha of .05 and achieving 80% power, a sample of 34 women is needed to detect a medium effect size.

H2c: *Increases in peptide response and subjective fullness will each mediate the relationship between fear and GI distress.*
Analytic Plan: Three mediation models will be tested with posited mediators (CCK response, PYY response, and subjective ratings of fullness) at 10 minutes after the meal mediating the relationship between subjective fear immediately before the meal and GI distress 20 minutes after the meal. These analyses will utilize data from the "high fat" test meal instruction.
Power Analysis: Using Monte Carlo simulation[18] and correlation estimates from our pilot data (r=.37 fear of food, eating and weight gain with postprandial fullness; r=.46 fear of food, eating, and weight gain and GI distress; r=.41 postprandial fullness and GI distress), 97 individuals are needed to detect a significant indirect effect of fullness at 80% power. In the absence of existing data for correlations of CCK and PYY with fear and GI distress, we will rely on the estimates from our pilot data. As such, 97 individuals are needed to test the hypotheses that CCK and PYY each mediate the relationship between fear of food, eating, and weight gain and GI distress.

Exploratory Analysis: A serial multiple mediation model will be examine fear as a cause of CCK and PYY increases and in turn, increases in fullness, GI distress, and urges to restrict food intake.
Analytic Plan: A path analysis will be fit using data from the high fat test meal. Self-reported fear immediately before the test meal will predict CCK response 10 minutes after the meal, which will predict self-reported fullness 20 minutes after the meal. Self-reported fullness 20 minutes after the meal will predict self-reported postprandial GI distress 30 minutes after the meal, and GI distress 30 minutes after the meal will predict self-reported urges to restrict food intake 60 minutes after the meal. CCK response 10 minutes after the meal will also predict postprandial GI distress 30 minutes after the meal. This same model will be repeated with PYY response in place of CCK response, as we anticipate that CCK and PYY response will be highly correlated.
Power Analysis: Based upon our pilot data and estimates described above, we will be underpowered to detect effects. This is an exploratory analysis.

References

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