

Hormones and Neurocircuitry of Appetite Regulation In Anorexia Nervosa:

Research Update

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AN is a Complex Genetic Disease

10-fold increased risk among first-degree relatives of AN vs. relatives of HC

Twin studies suggest 55-75% heritability

Likely multiple genes of modest effect interacting w/environment

Few data:

- Most candidate studies have focused on DA, 5-HT, and feeding regulation pathways
- Mixed findings - in general, vastly underpowered, not replicated

Several studies have suggested that genes mediating appetite/satiety (preproghrelin, ghrelin R) are associated with eating disorders

AN Affects Young Women, Associated with Morbidity and Mortality

Complications

- Endocrine
 - GH resistance, hypogonadism, hypercortisolemia
 - **Abnormalities in appetite regulating hormones**
 - Osteoporosis

Appetite-Regulating Hormones and AN

Some alterations are expected adaptation to starvation

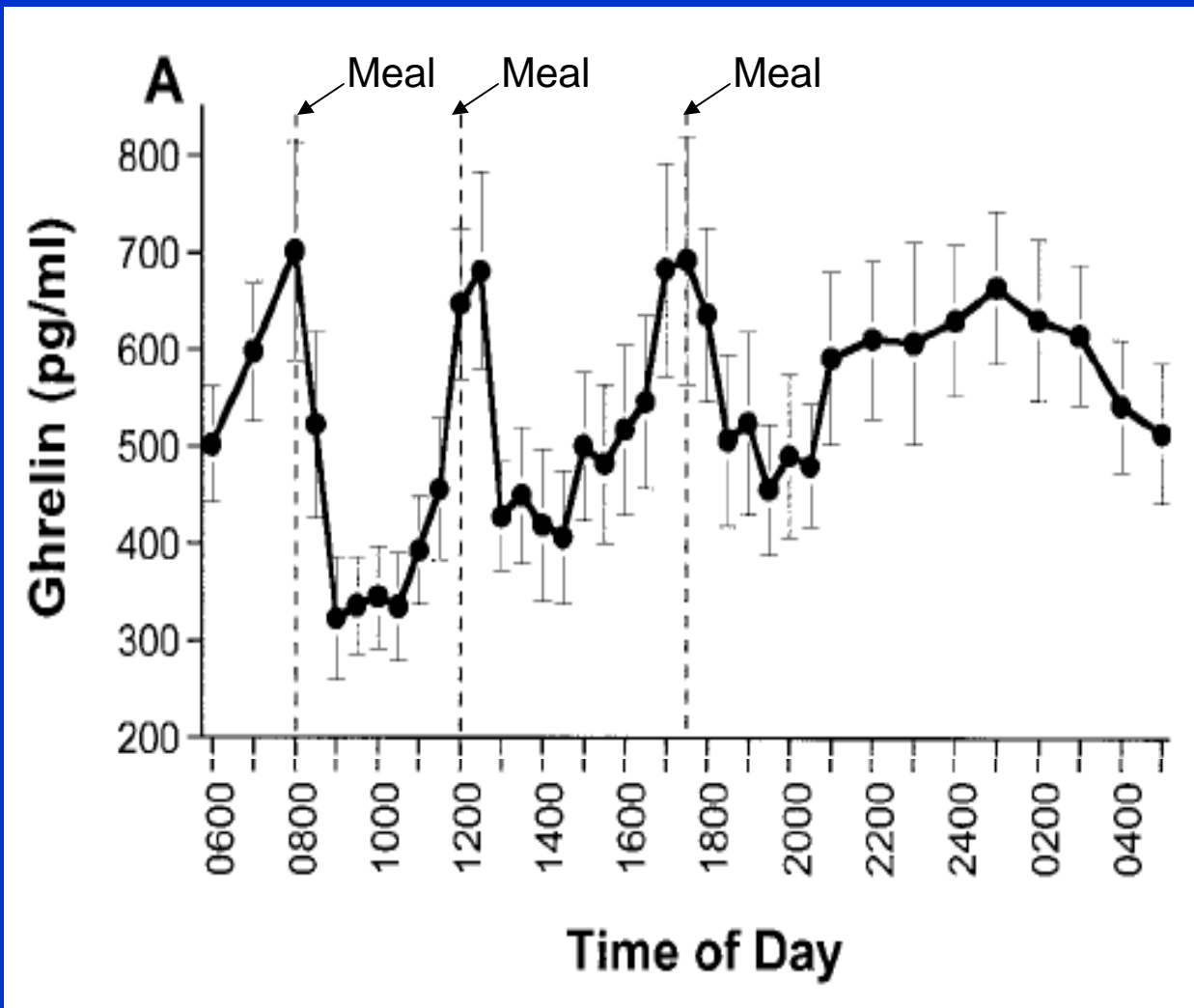
Ghrelin- levels of this hormone made by the stomach that **stimulates eating are high**

Others may be paradoxical-

PYY- levels of this hormone made by the intestine that **reduces appetite are also high**

Persistence of abnormalities post-recovery raises question of etiologic role

Normal Physiology: Ghrelin Falls After Meals, Increases Between Meals



Cummings et al. Diabetes 2001



Ghrelin Increases Appetite and Caloric Intake

Fasting AM IV bolus 100mcg ghrelin normal subjects followed by assessment of appetite, visualization of food one hour later; same experiment w/placebo the next day

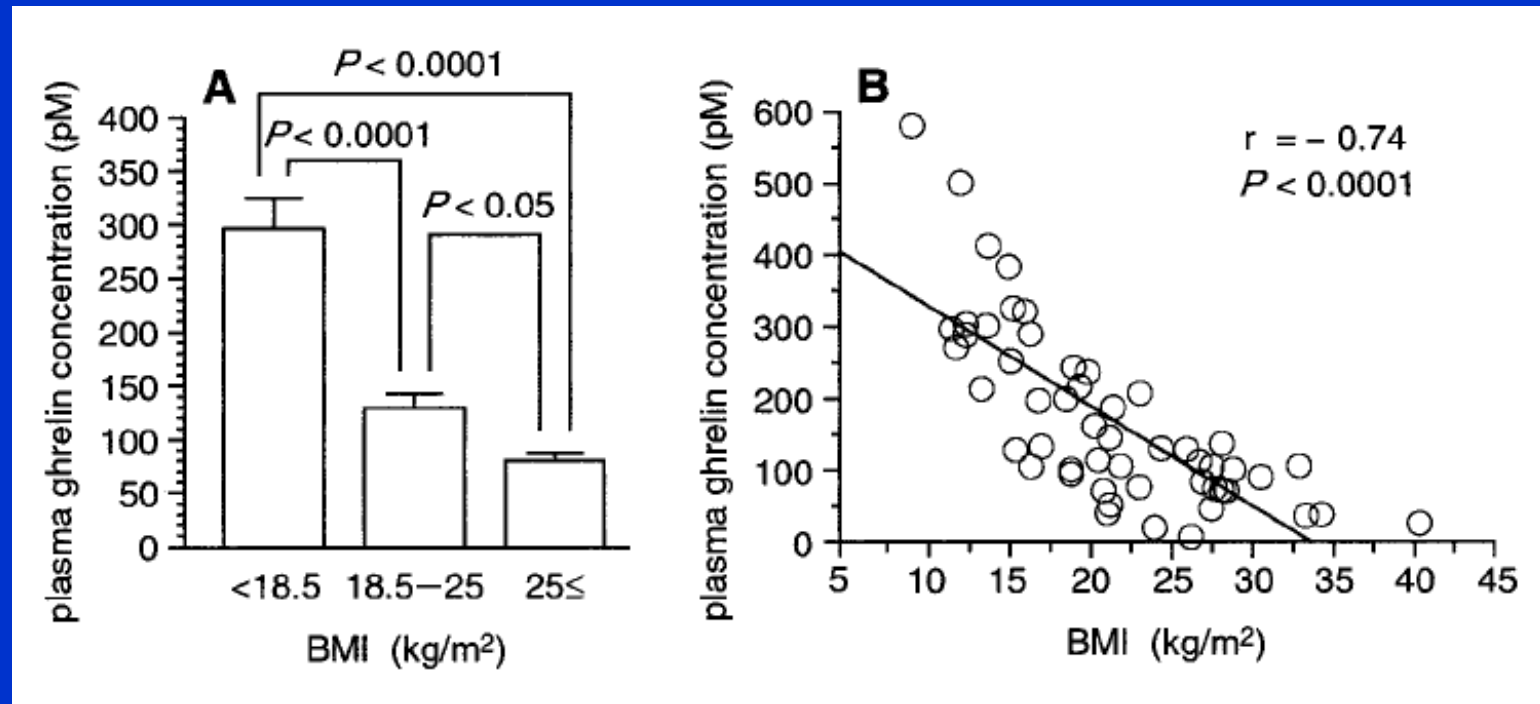
- Sig increase in appetite after ghrelin
- Most reported a vivid visualization of their preferred meal after ghrelin

Neuropsychopharmacology 2005)

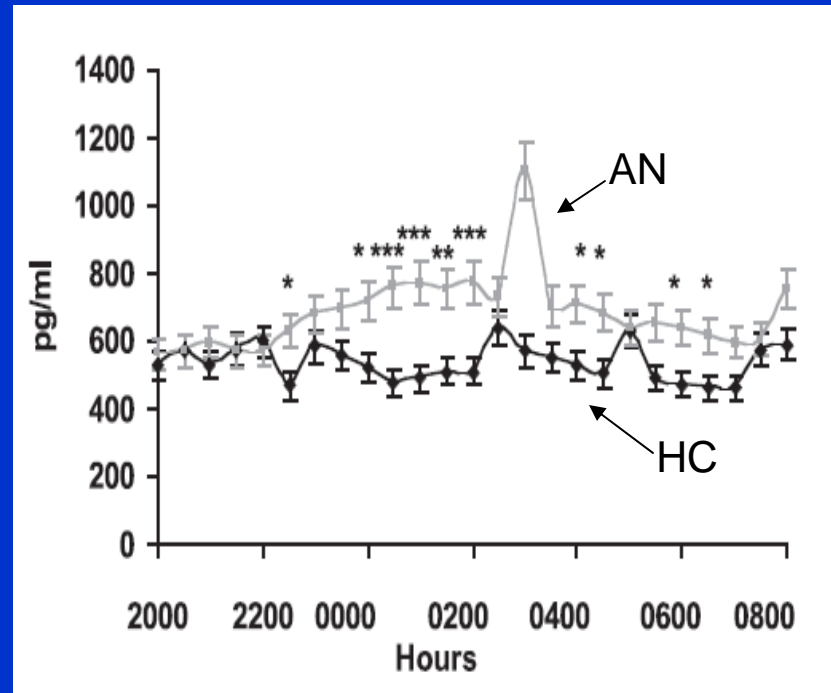
Others have reported increased caloric intake (Wren et al. JCEM 2001)

Ghrelin and BMI

Fasting ghrelin levels in 28 HC (14 F, 14 M), 17 AN (16 F, 1 M),
11 obese (7 F, 4 M)

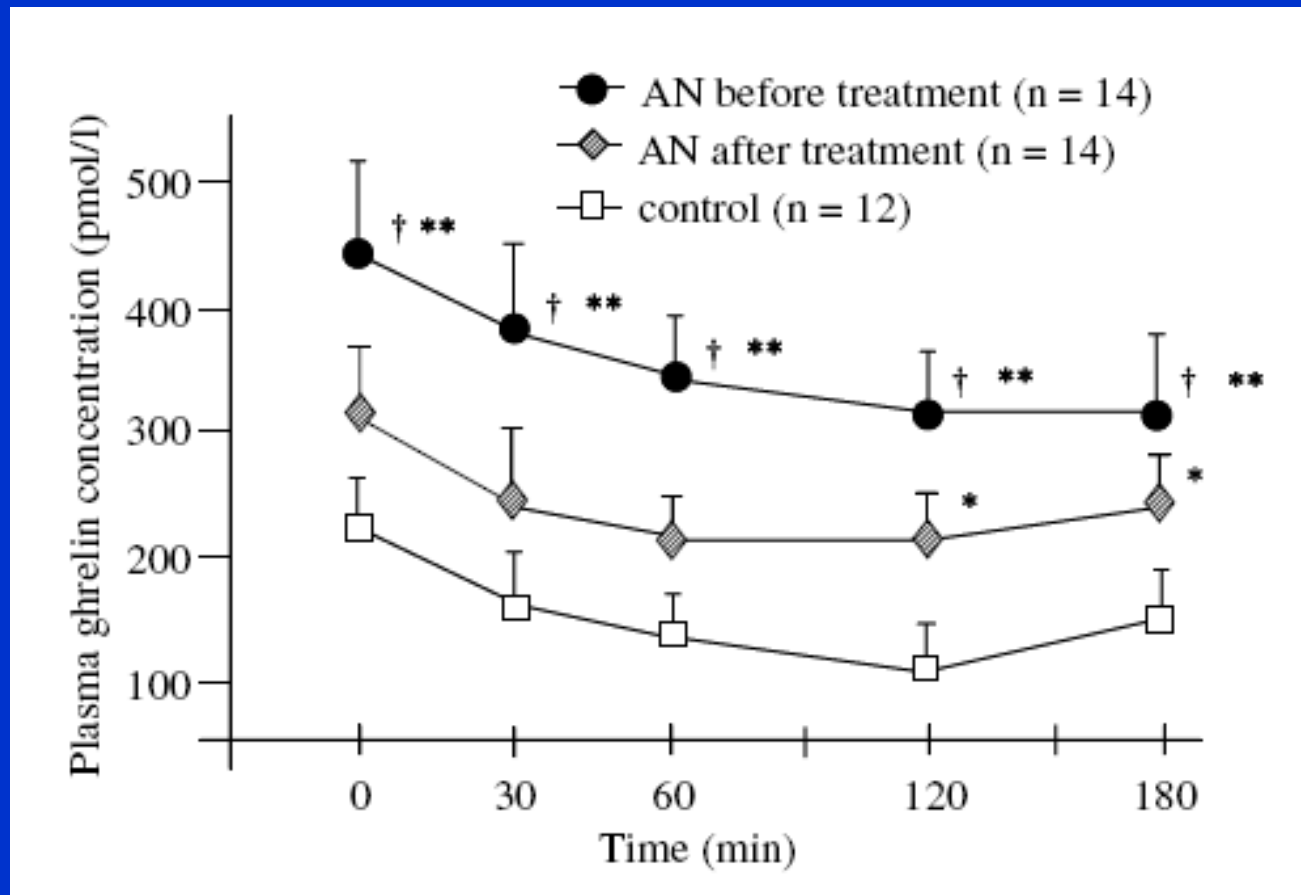


Elevated Ghrelin in AN

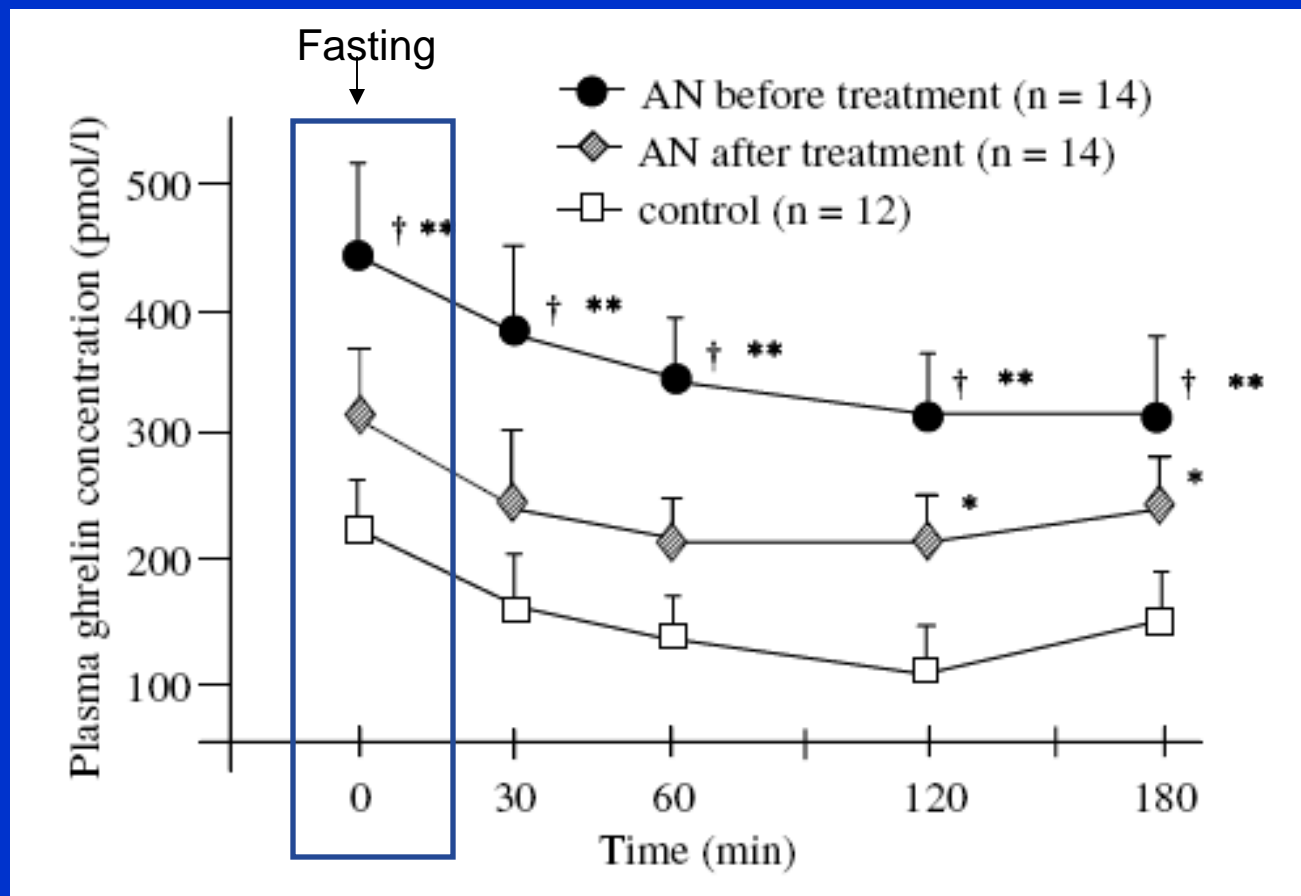


Misra et al. AJP-Endo 2005

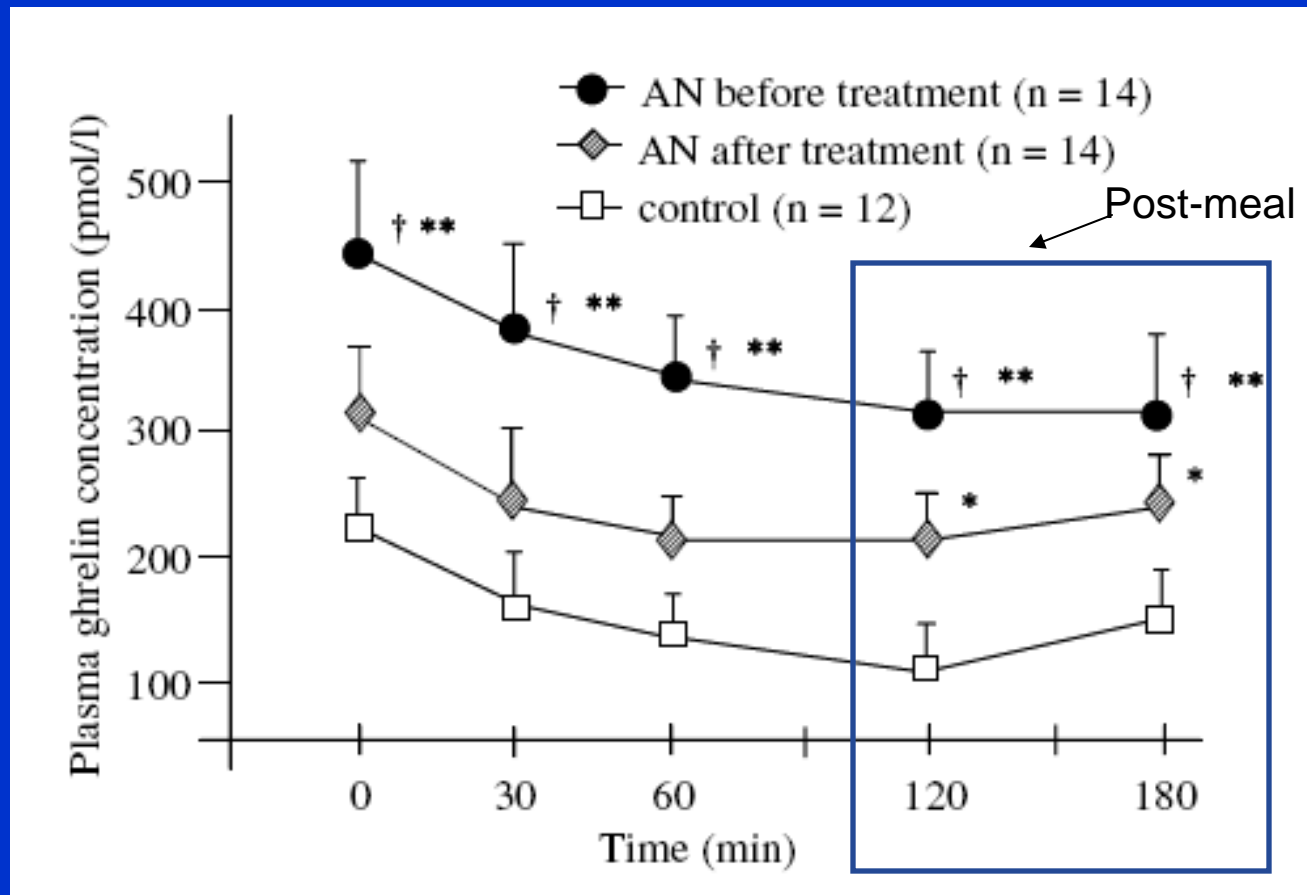
Persistent Abnormalities in Ghrelin Post-Recovery



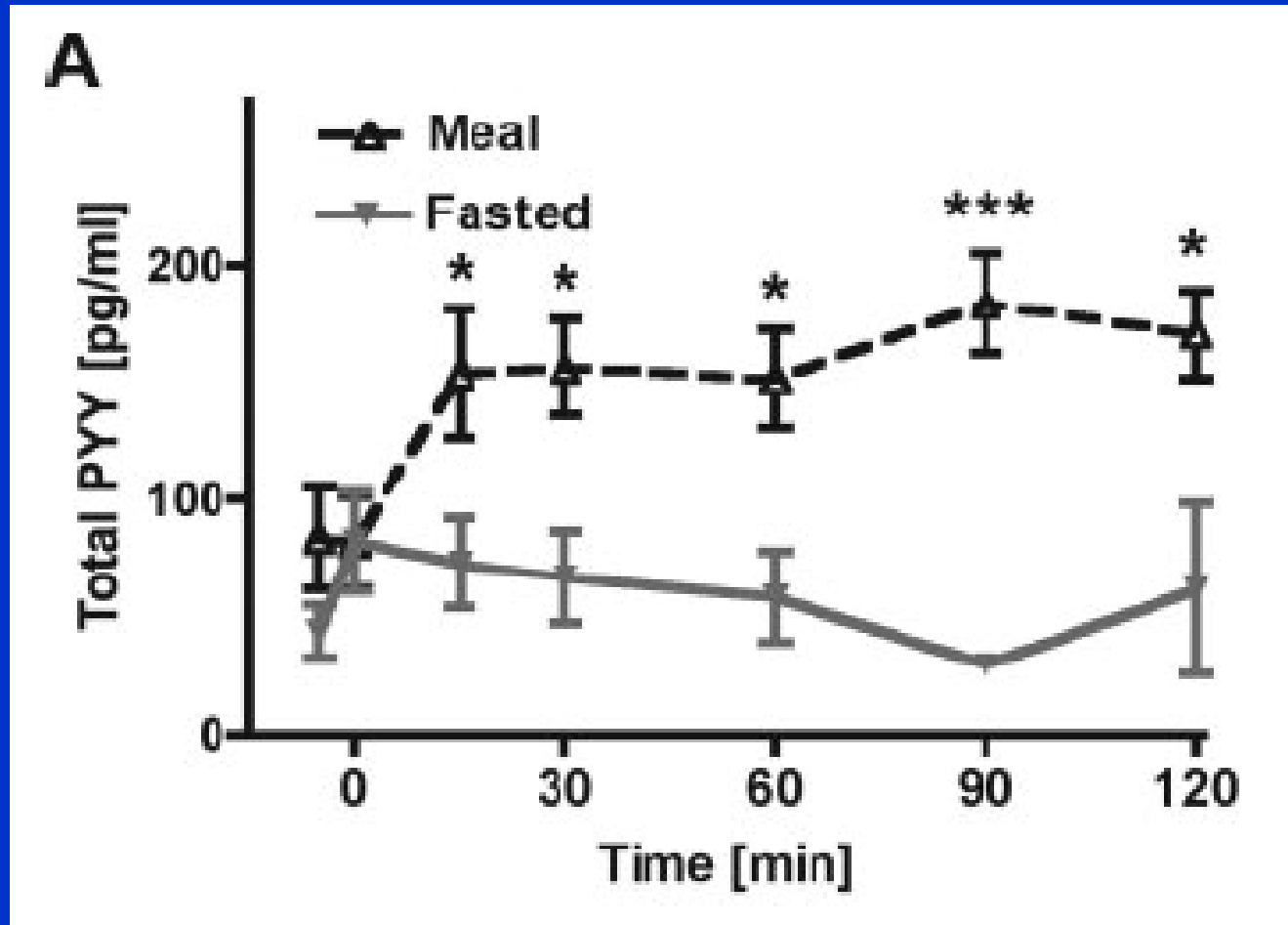
Persistent Abnormalities in Ghrelin Post-Recovery



Persistent Abnormalities in Ghrelin Post-Recovery

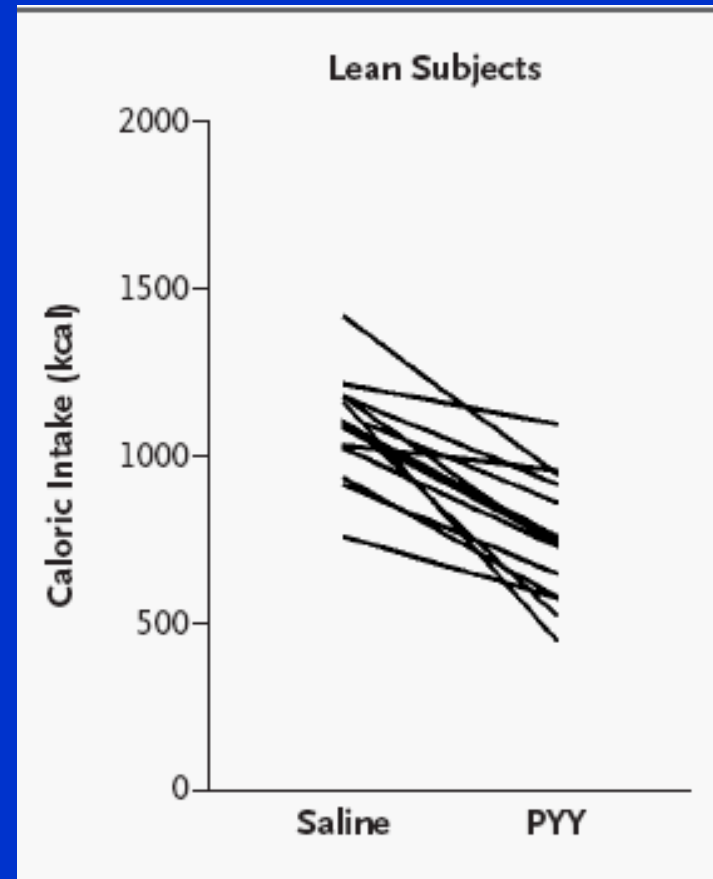
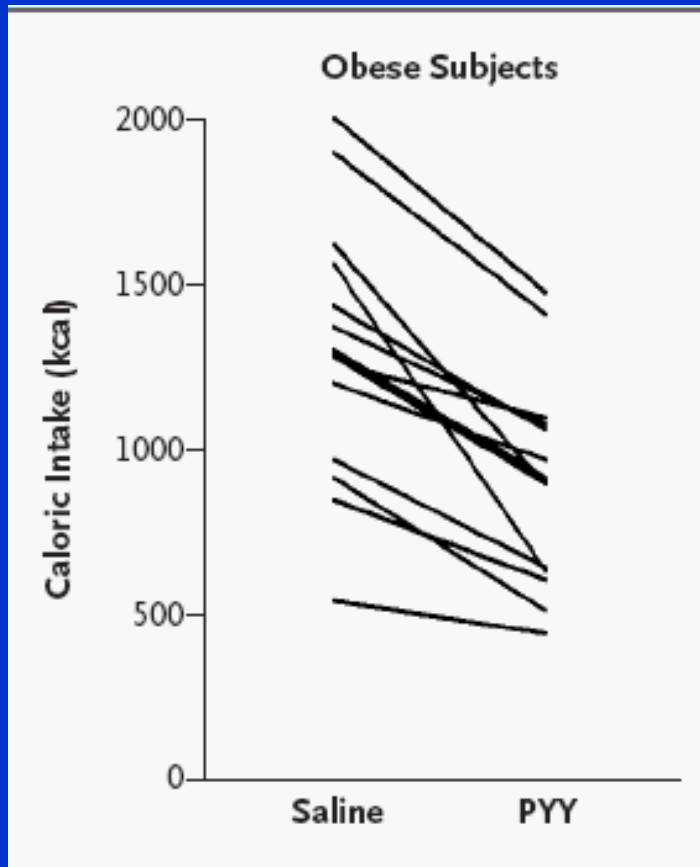


Normal Physiology: PYY Rises After Food Intake



Pfluger et al. JCEM 2007

PYY Reduces Appetite and Caloric Intake

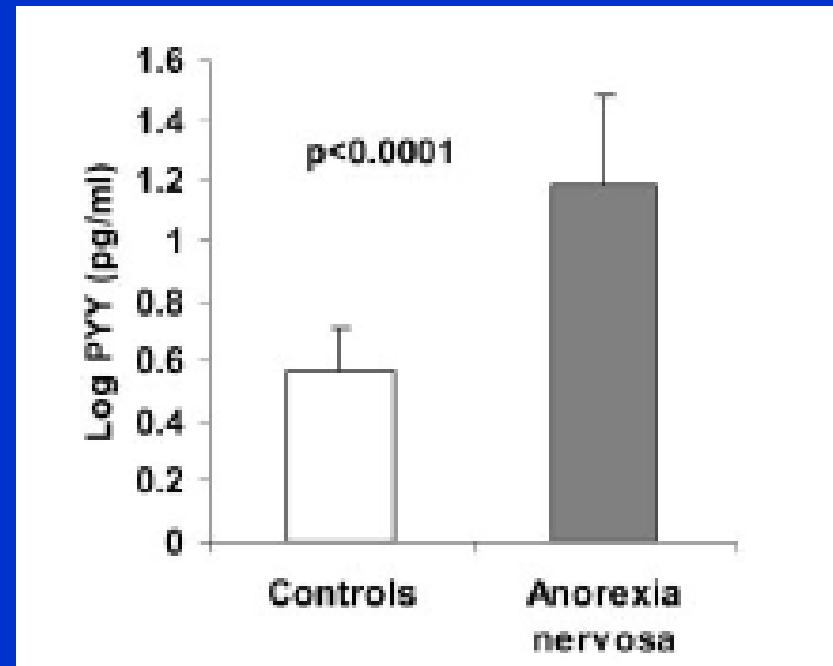


PYY Levels are High in AN

PYY predicts

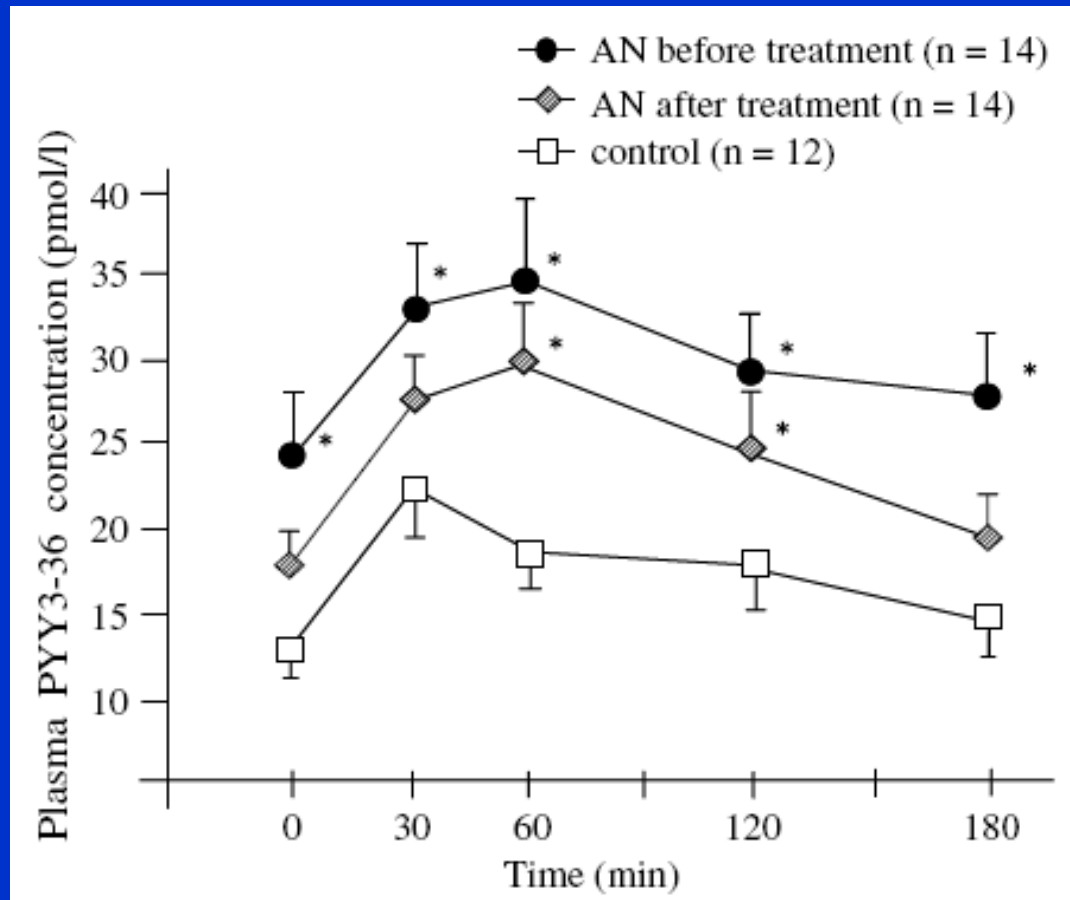
- Lower intake of fat
- Lower caloric intake
- Lower BMI
- Lower fat mass

PYY does not normalize
with recovery

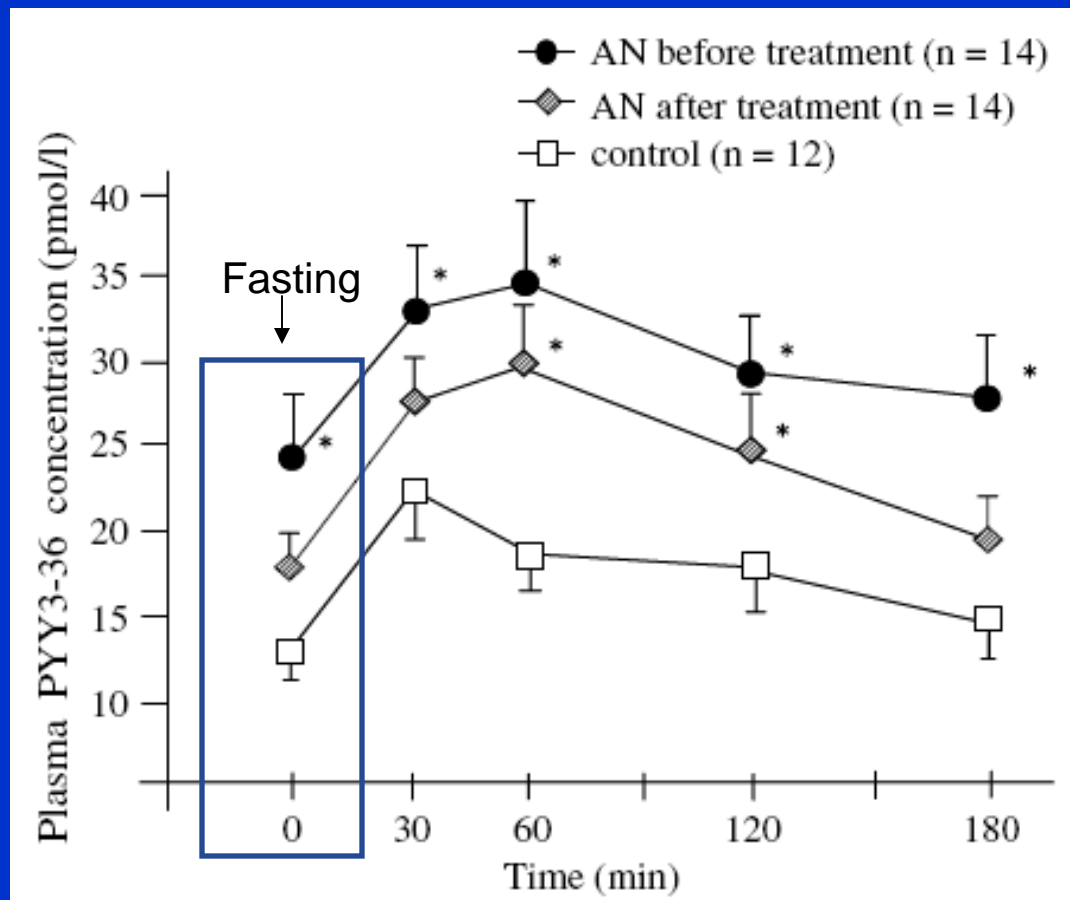


Misra et al. JCEM 2006

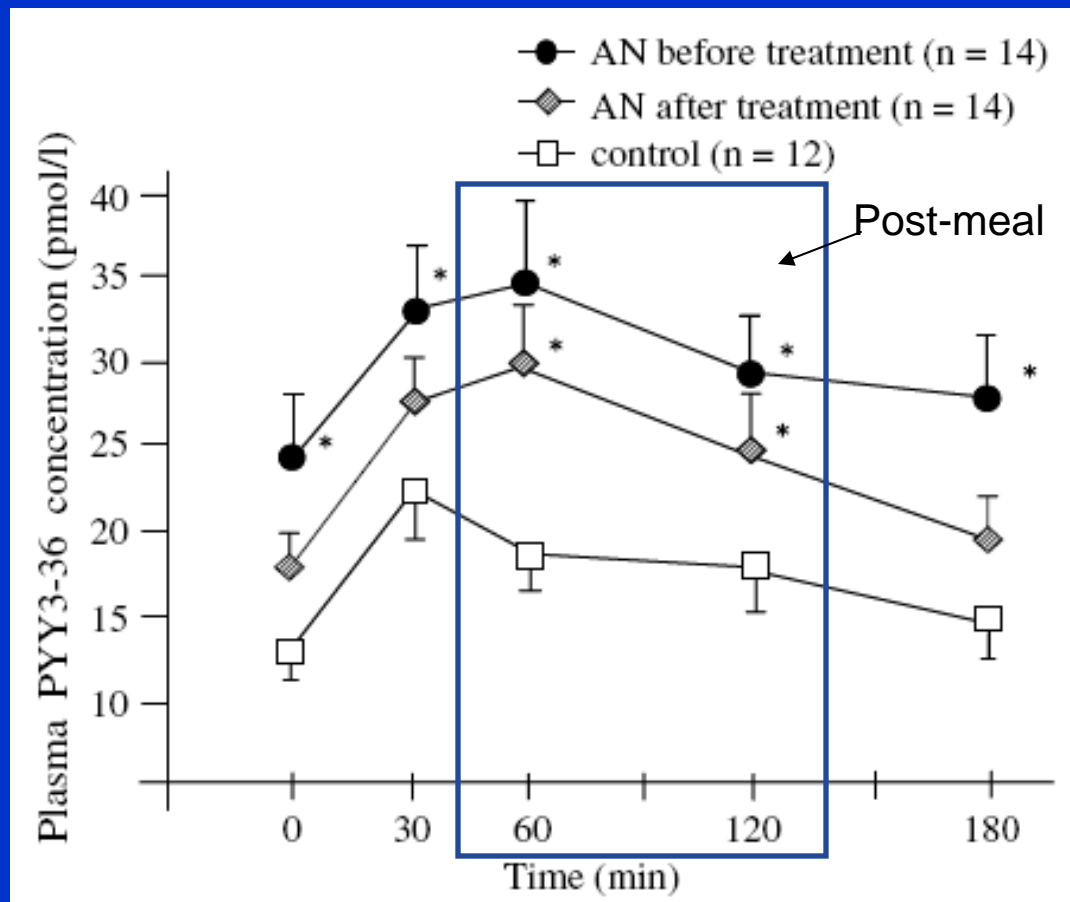
Persistent Post-Meal Abnormalities in PYY Post-Recovery



Persistent Post-Meal Abnormalities in PYY Post-Recovery



Persistent Post-Meal Abnormalities in PYY Post-Recovery



Hypotheses

1. Response of appetite-regulating hormones to consumption of a mixed meal is abnormal in AN compared to controls.
2. Using fMRI, brain activity in regions implicated in appetite regulation and food motivation circuitry will be abnormal in AN compared with healthy controls both pre- (a) and post (b)- meal intake.
3. Hormone abnormalities correlate to brain activity deficits.



Study Design: 20 AN, 20 AN-R, 20 HC

Key Enrollment Criteria: 18-25 yrs, no contraindication to MRI

- **AN:** DSM-IV criteria, <85% IBW, amenorrheic, restrictive subtype, no significant binge/purge history, no antipsychotics
- **AN-R:** DSM-IV criteria, restrictive subtype, no significant binge/purge history, no antipsychotics, maintenance of 90-110% IBW and regular menses >6 months
- **HC:** 90-110% IBW, regular menses, no sig psychiatric or disordered eating hx

Study Protocol

Pre-screening
& Screening
visit

Main visit

Questionnaires
Pre-scan 1

Questionnaires
Post-scan 1

Questionnaires
Pre-scan 2

Questionnaires
Post-scan 2

Pre-meal
fMRI

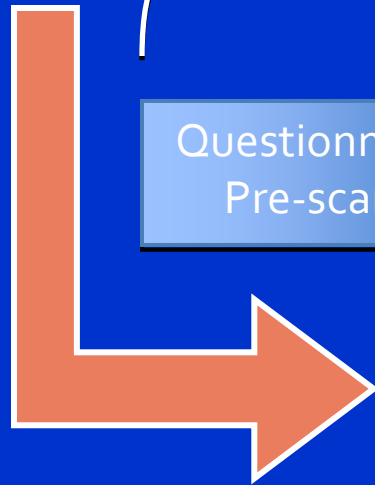
Standardized
meal

Post-meal
fMRI

Fasting baseline
blood draw for
hormone levels

Blood draws at 0, +30,
+60, +120 min

Bionutrition
Assessment



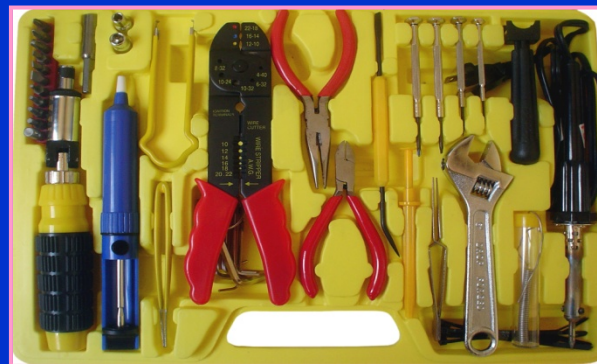


fMRI Paradigm

High Calorie – sweet



Object



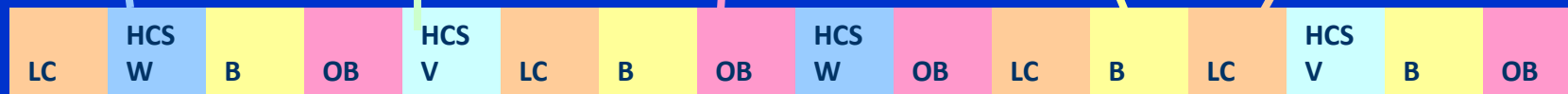
Low Calorie



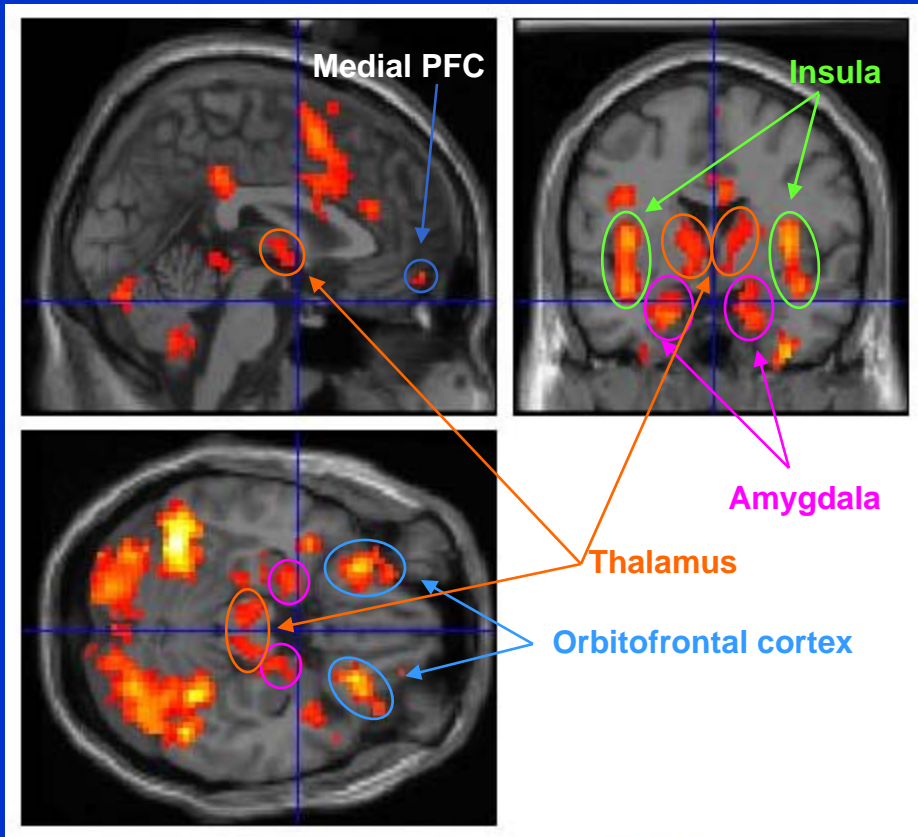
High Calorie – savory



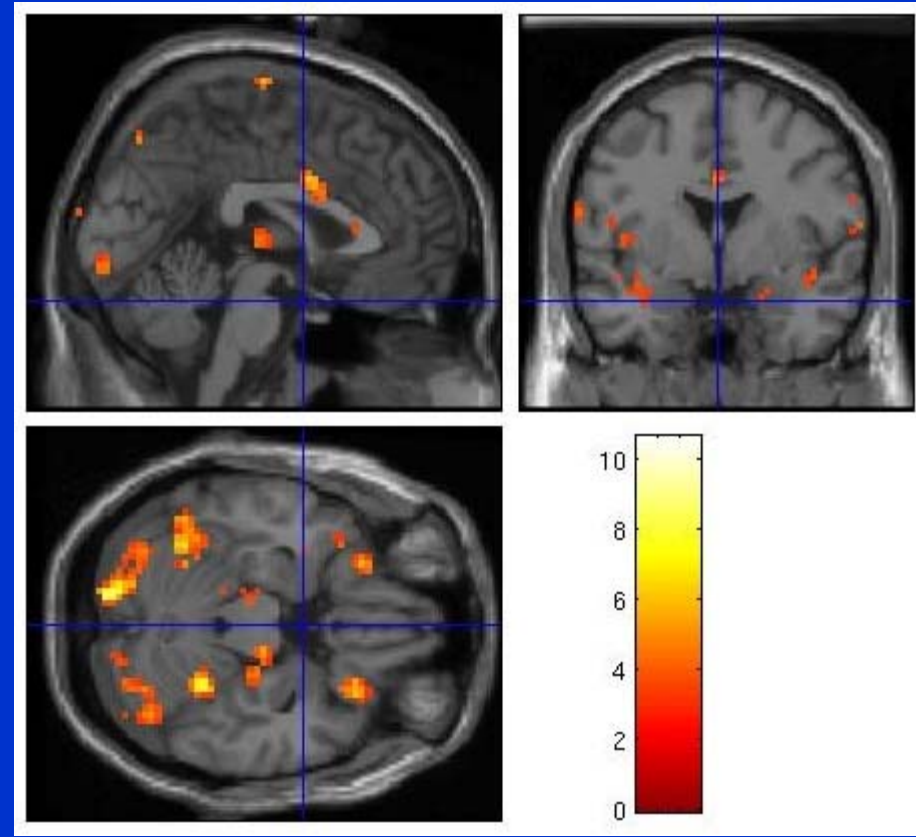
Baseline



Pre-meal



Post-meal



Amygdala: Emotion

Orbitofrontal Cortex: Reward

Medial Prefrontal Cortex: Visceral

Insula: Taste

Thalamus: Relay w/cortex



Summary/Conclusions

This study explores alterations in appetite-regulating hormonal pathways and associated neurocircuitry in AN

Preliminary data indicate that the paradigm is effective, and there appear to be differences in activation in AN vs. HC

Actively recruiting women ages 18-25 with current or past history of restrictive AN

Goal is to increase our understanding of how appetite-regulating pathways may be involved in the pathogenesis of AN, leading to potential therapies

