

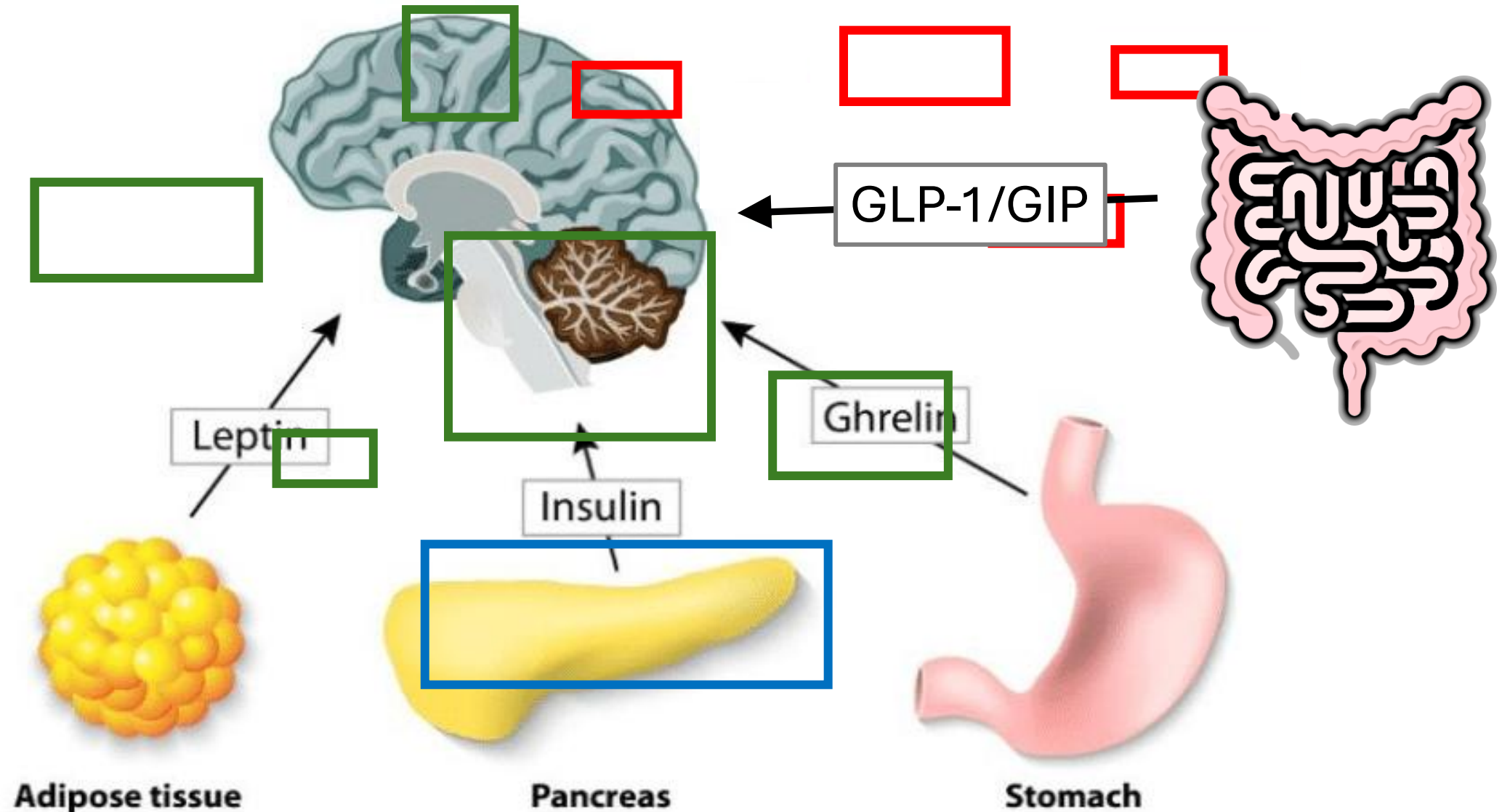
Neurobiology of Obesity

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Harvard Medical School

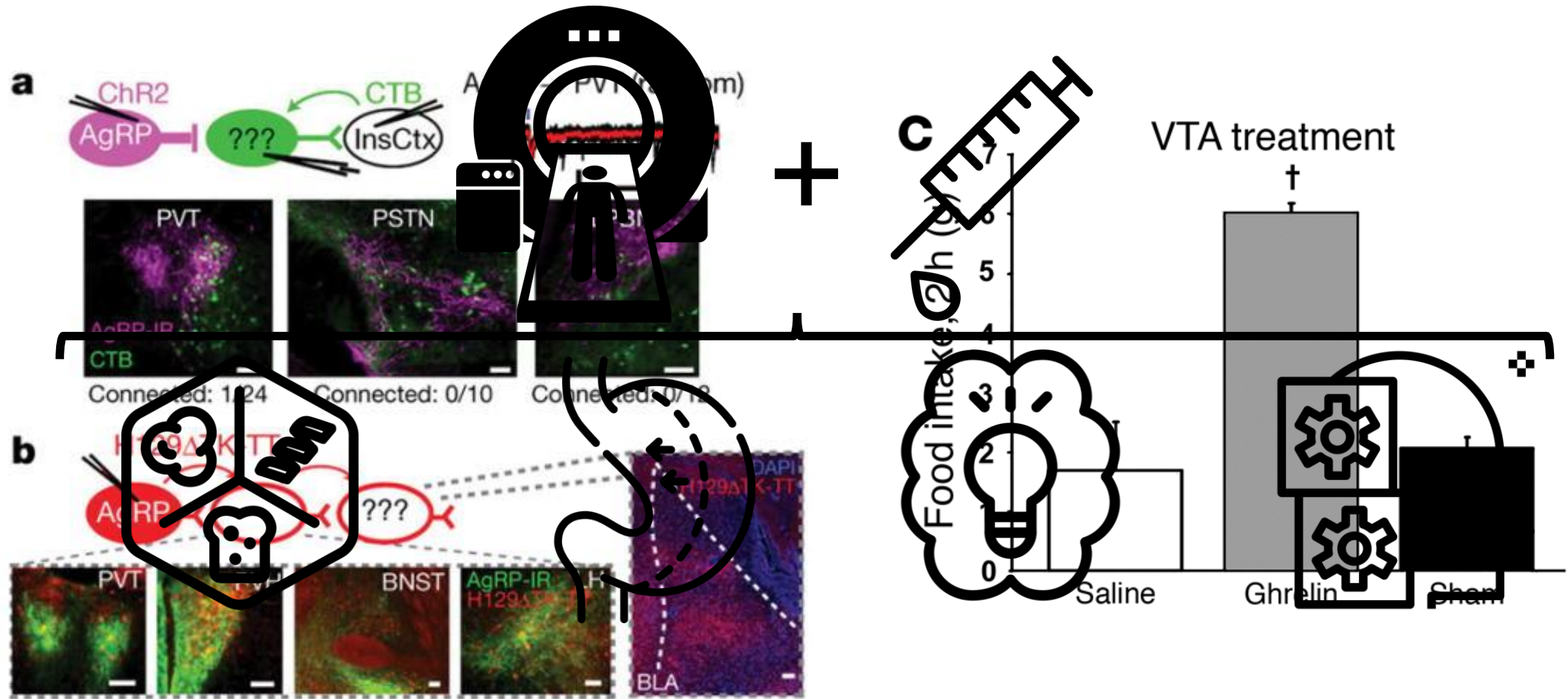
Disclosures

Neither I nor my spouse/partner has a relevant financial relationship with a commercial interest to disclose.

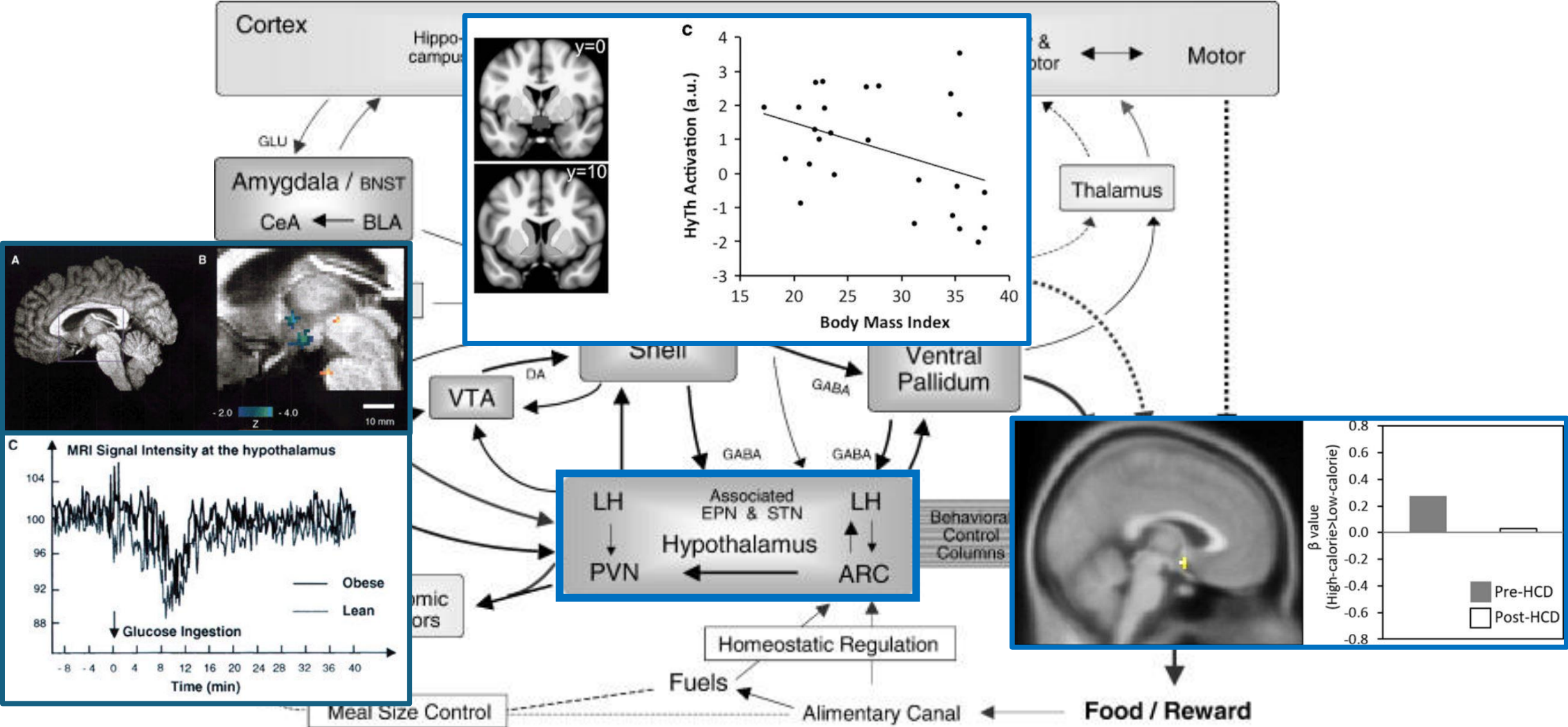
Networks governing food intake and appetite are highly complex and redundant



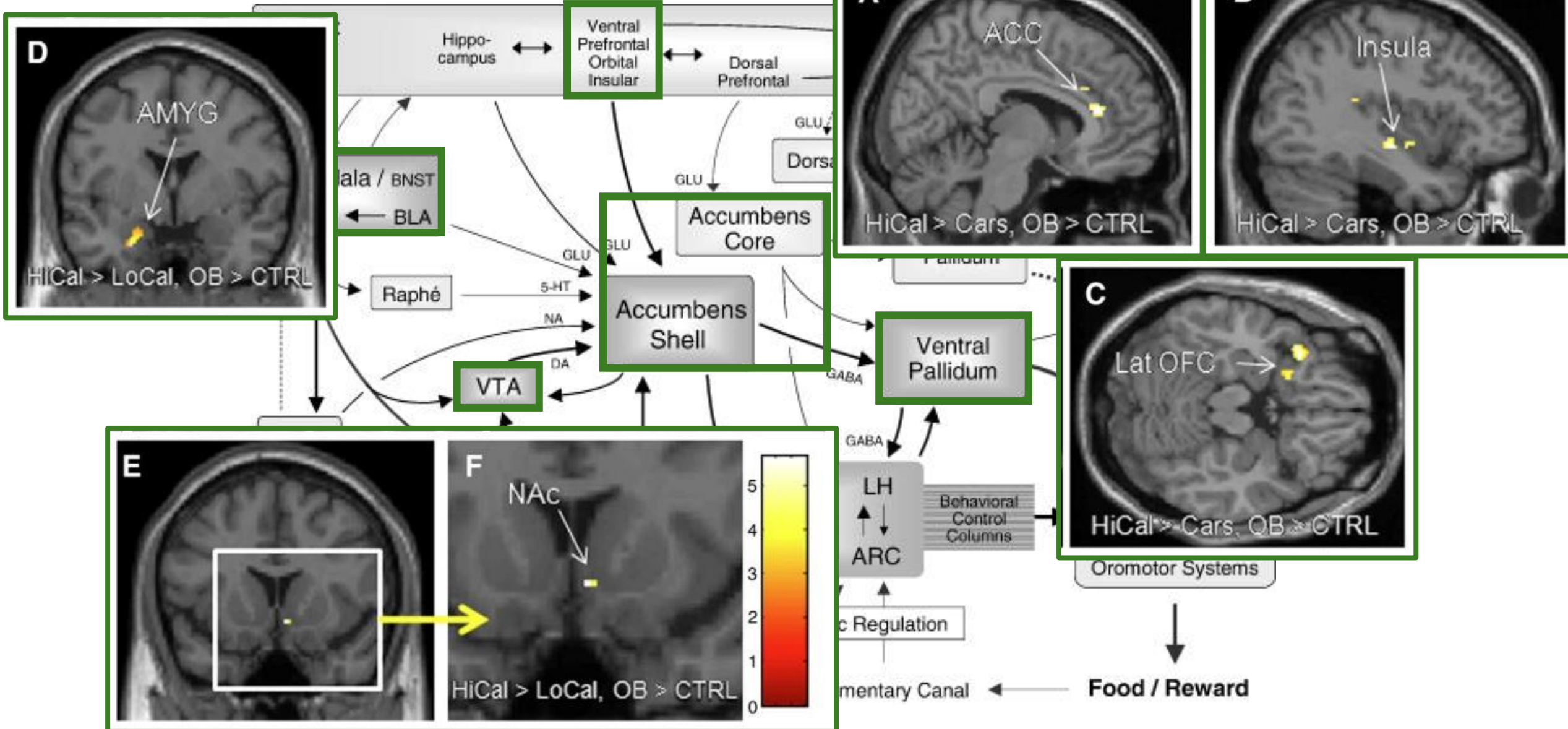
Noninvasive neuroimaging reveals insights into homeostatic and hedonic networks governing appetite in humans



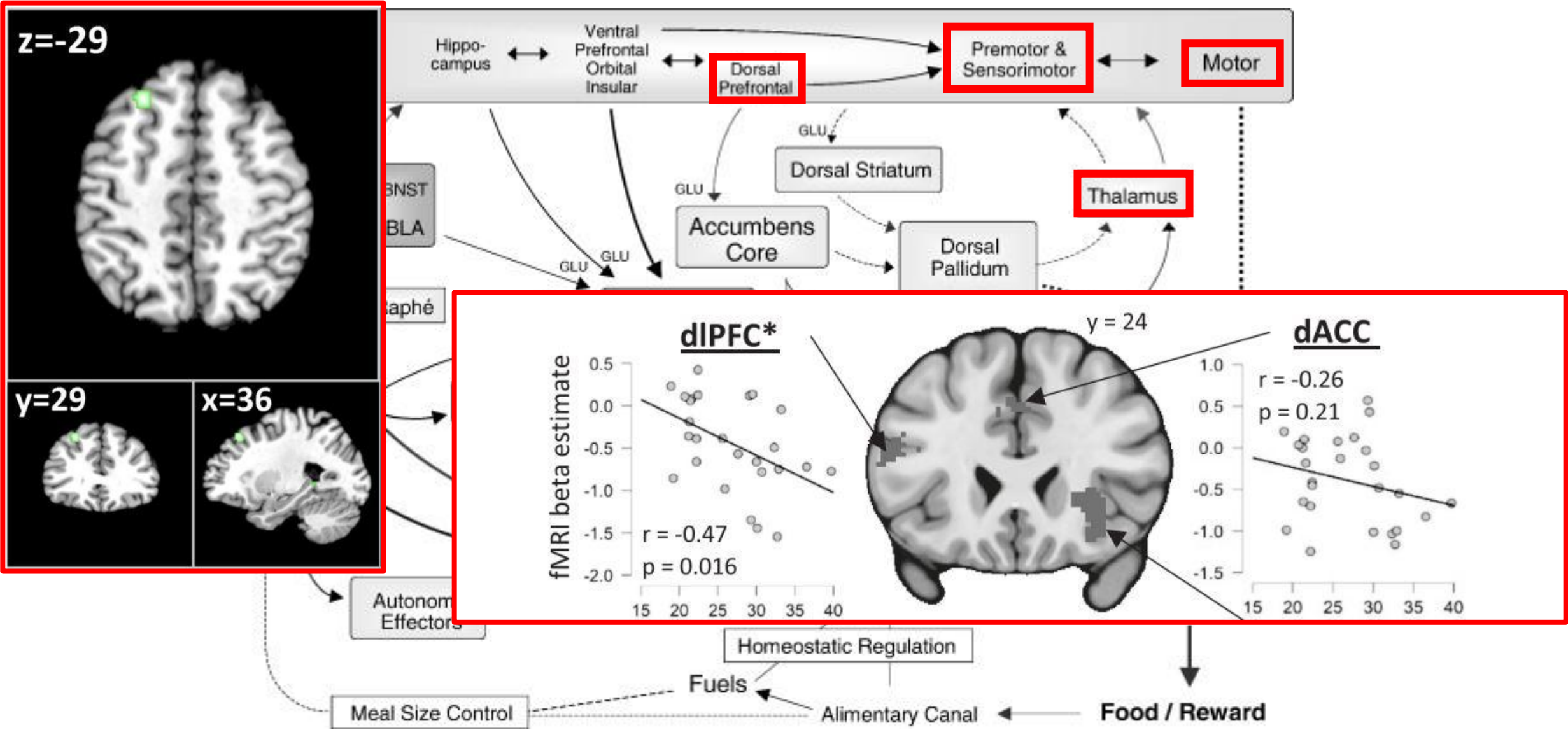
Obesity is associated with differential activation in homeostatic, reward, and cognitive control circuitry



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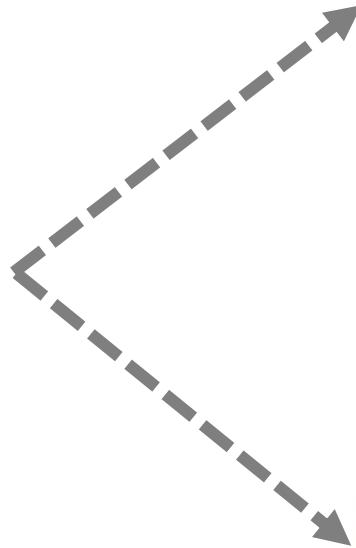


What drives weight regain following diet adherence?

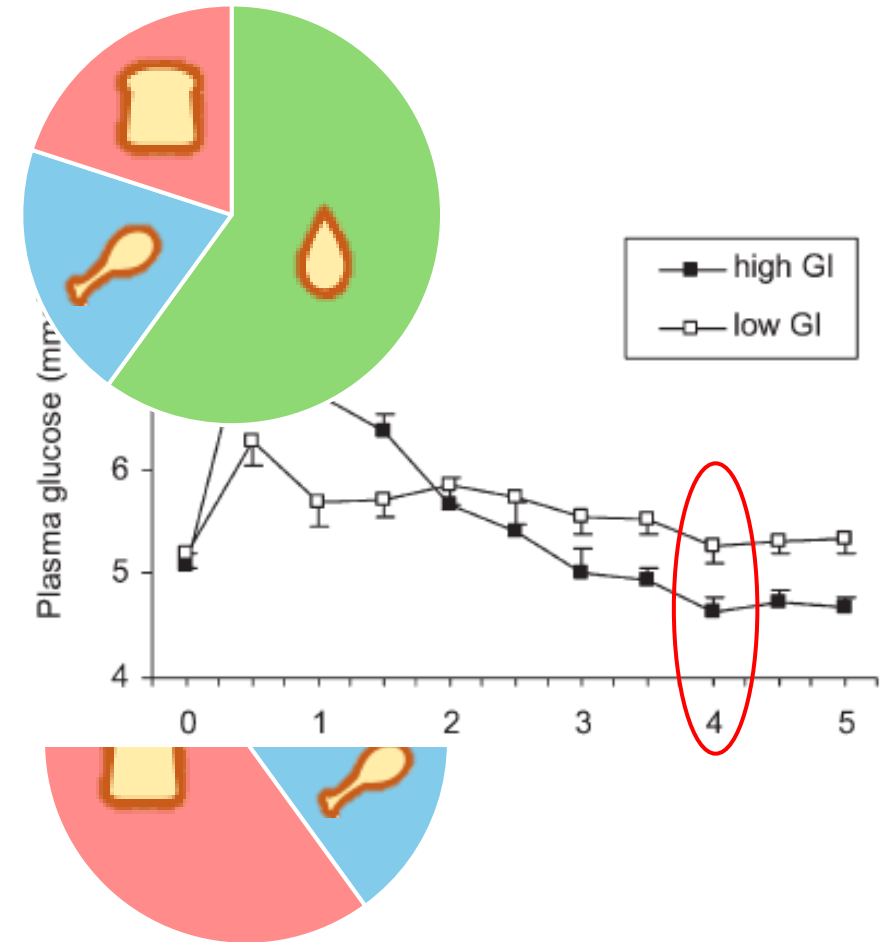
2000 cal



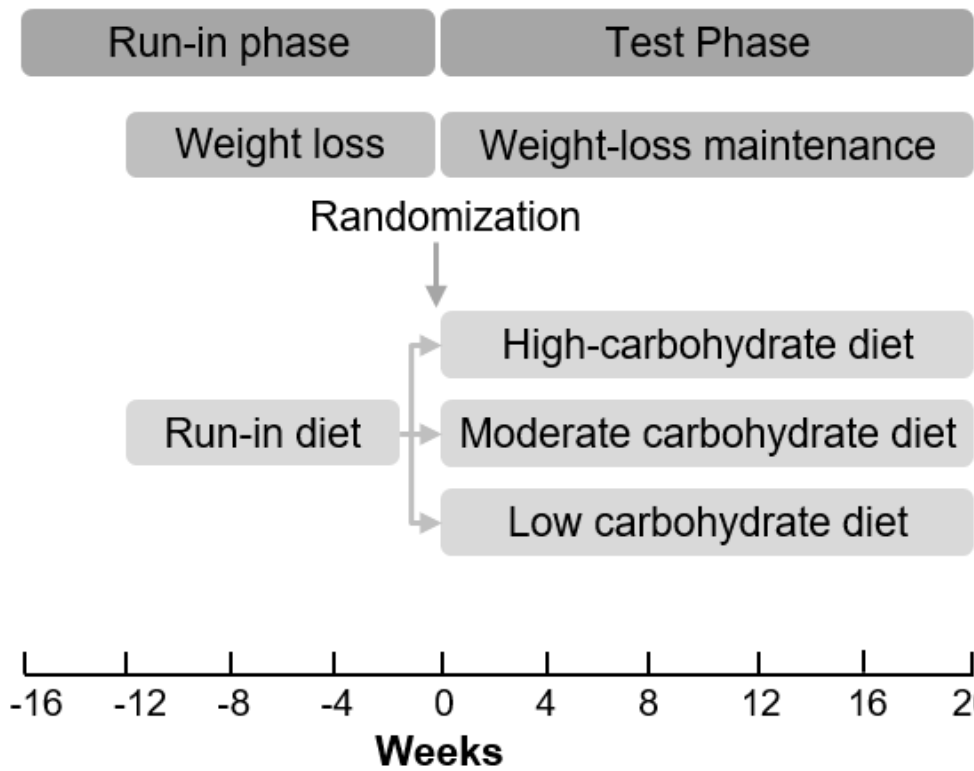
1500 cal



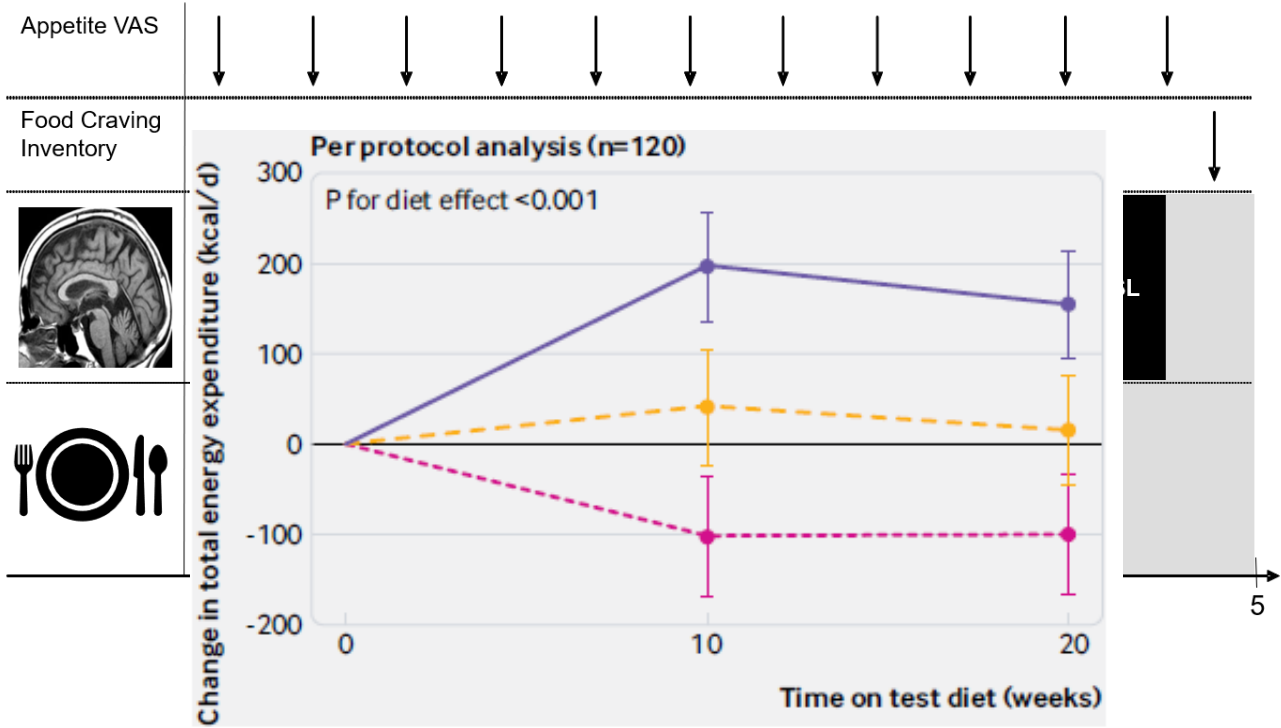
1500 cal



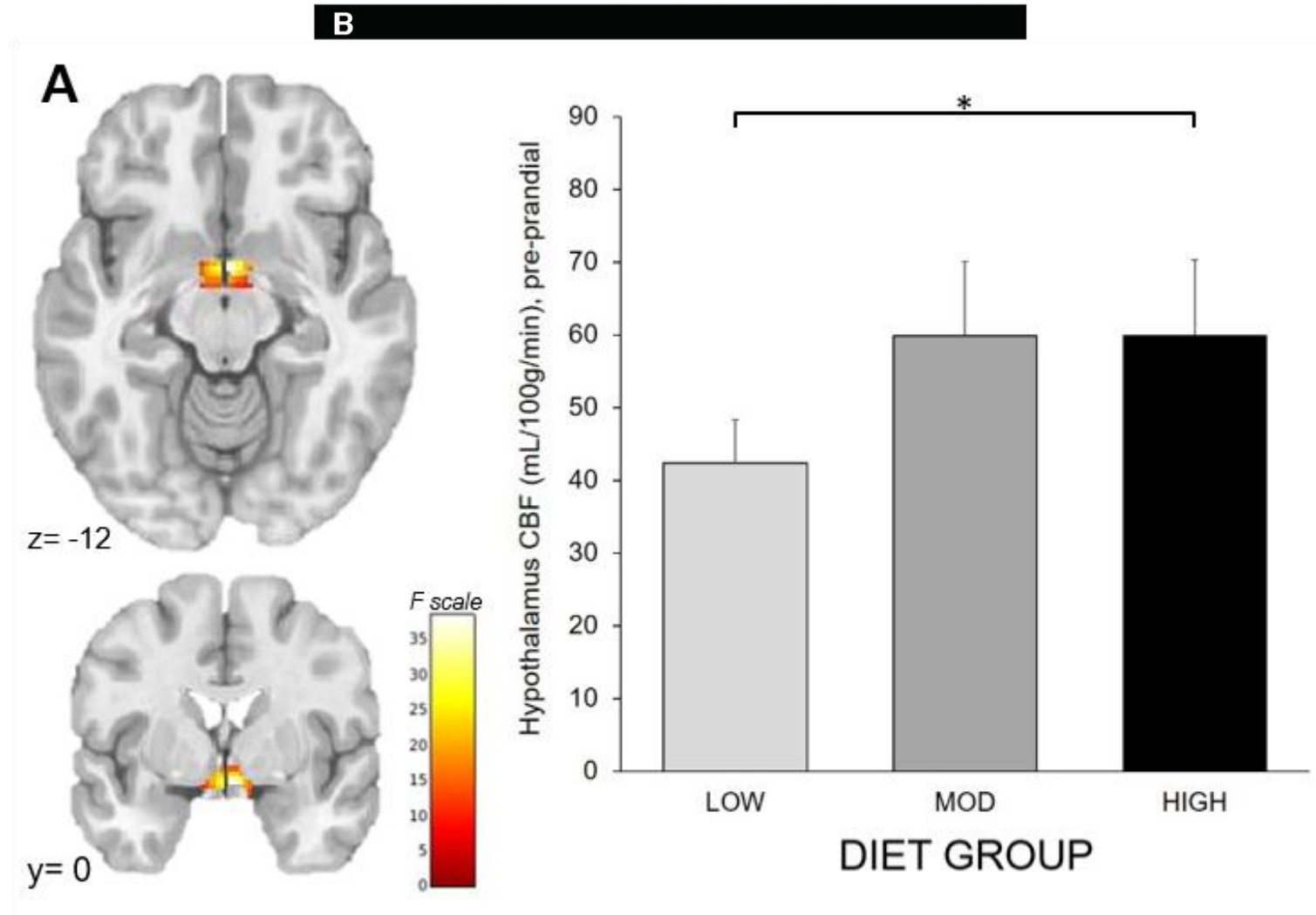
The (FS)² study was designed to examine effects of macronutrient diets on primary and secondary outcomes



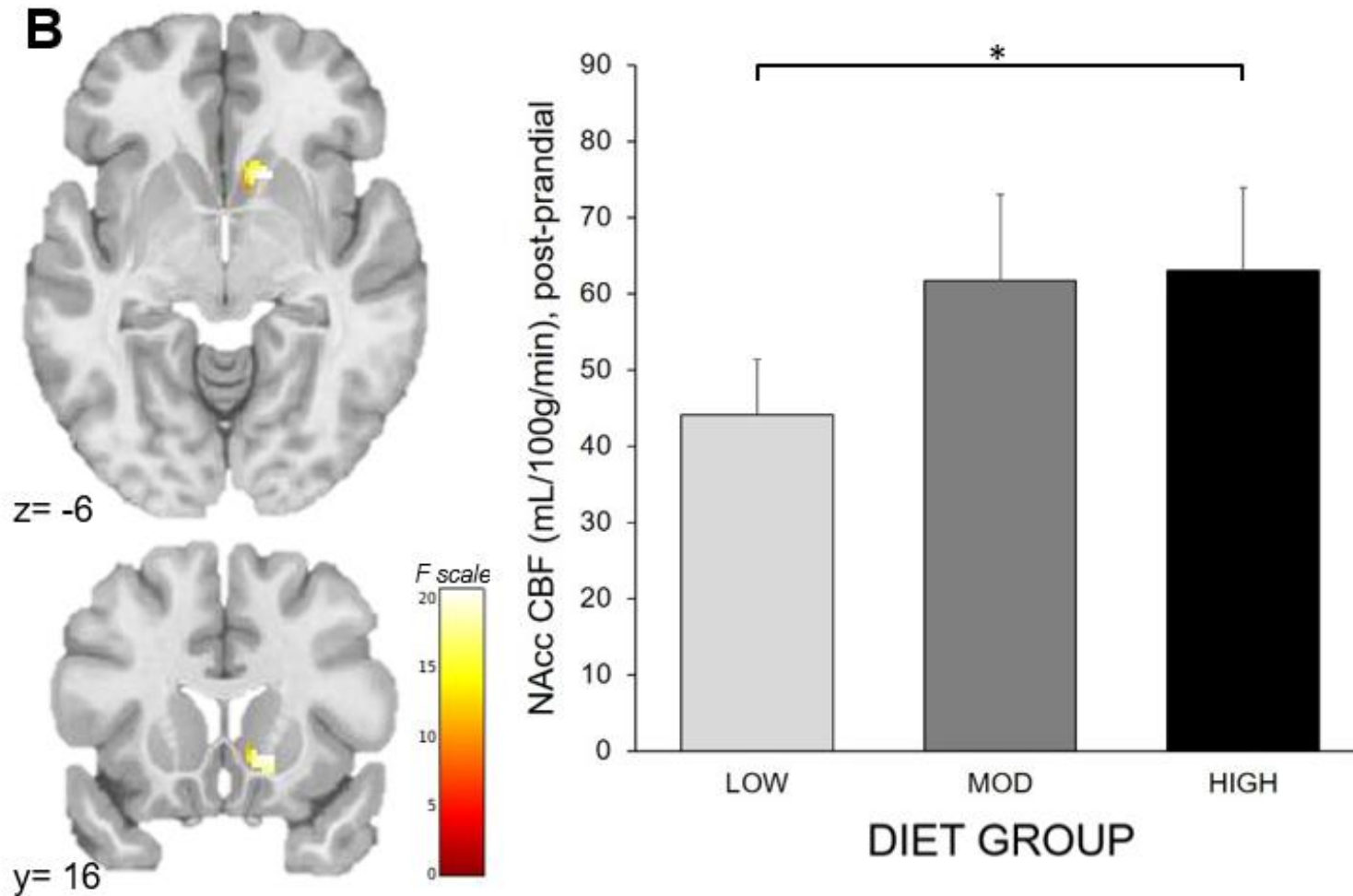
Dietary variable	Test Meal/Diet		
	HIGH	MOD	LOW
Carbohydrate (% of total energy)	60	40	20



Individuals randomized to low- vs. high-carbohydrate diets showed lower preprandial blood flow to the hypothalamus and other regions

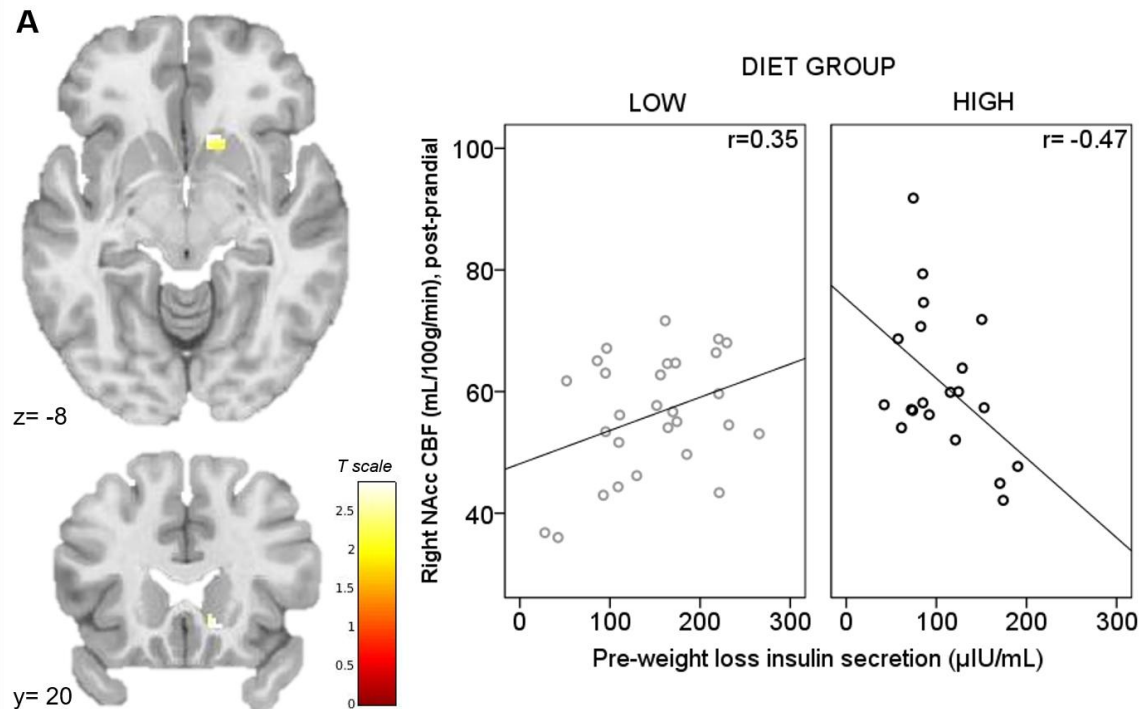


Individuals randomized to low- vs. high-carbohydrate diets showed lower postprandial blood flow to the NAcc

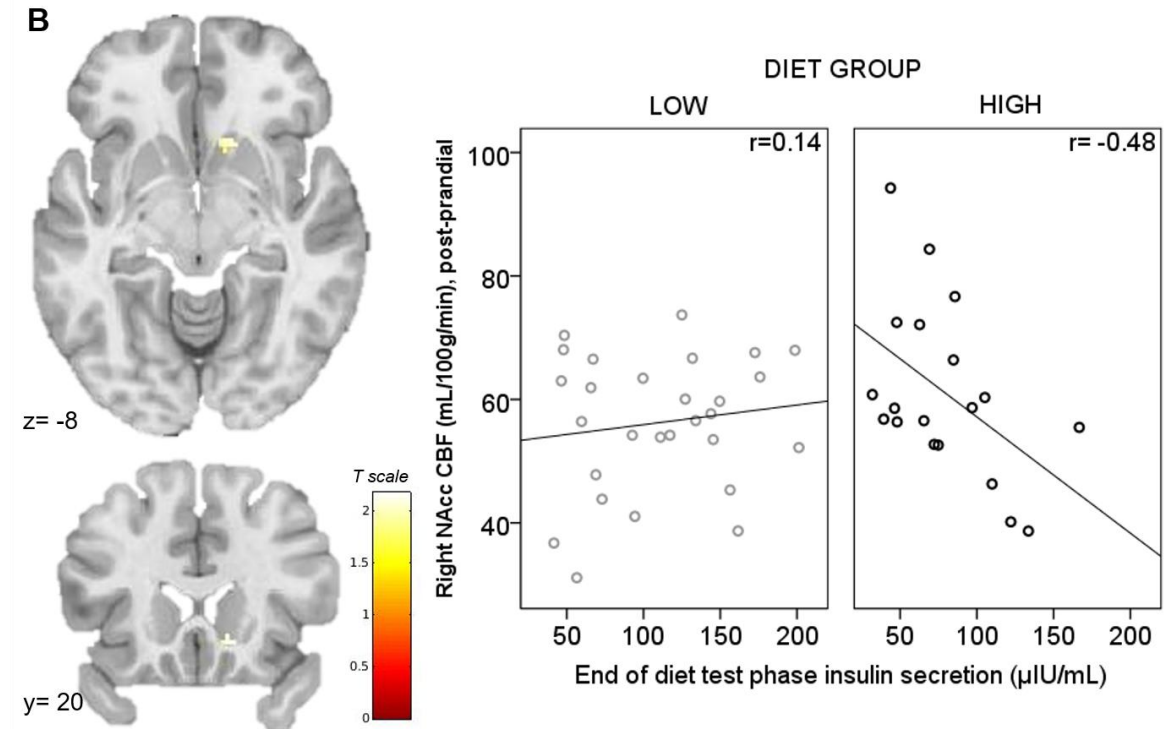


Pre-weight loss and end of test phase insulin secretion modified the relationship between diet group and postprandial NAcc blood flow

Pre-weight loss insulin-30

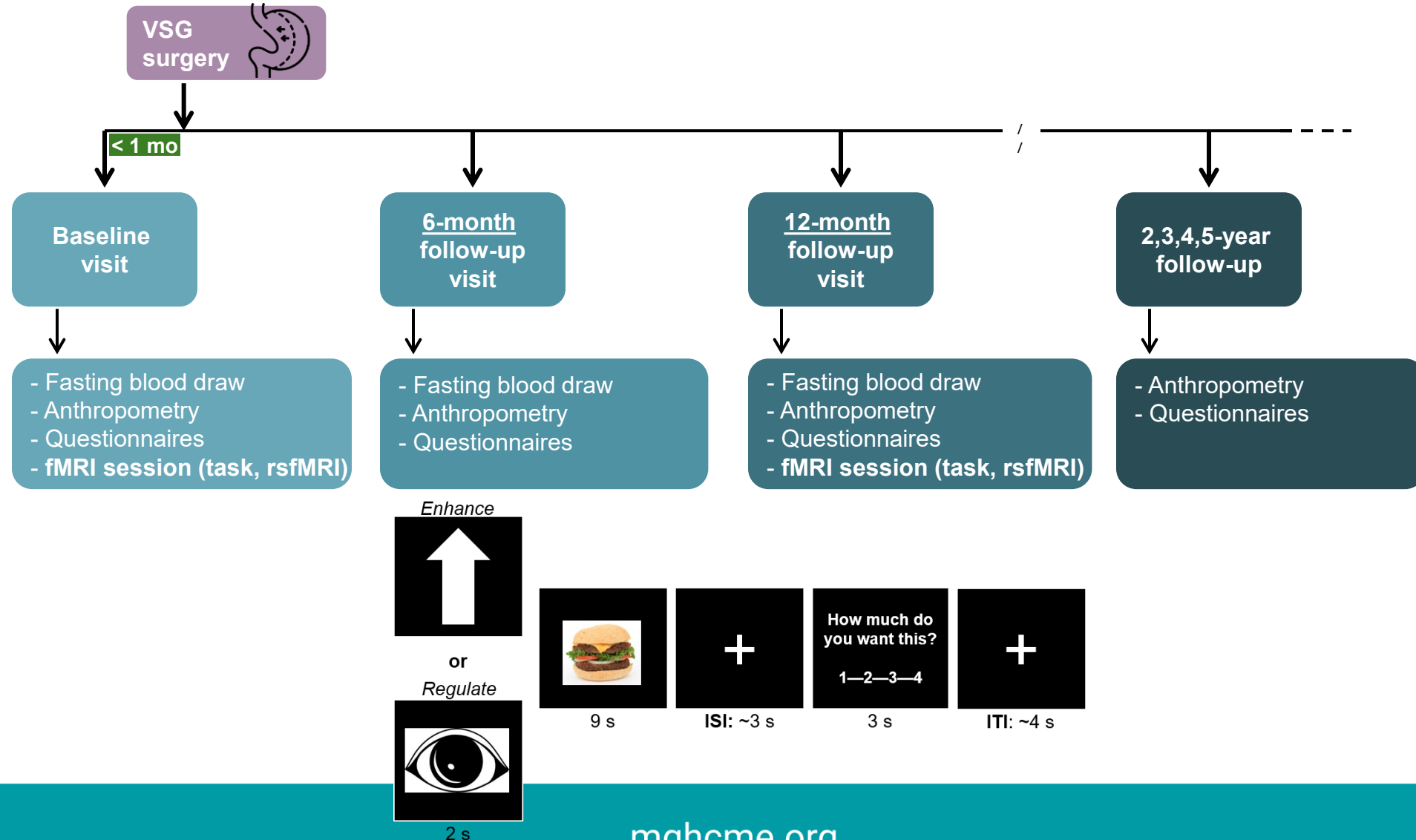


End of test phase insulin-30

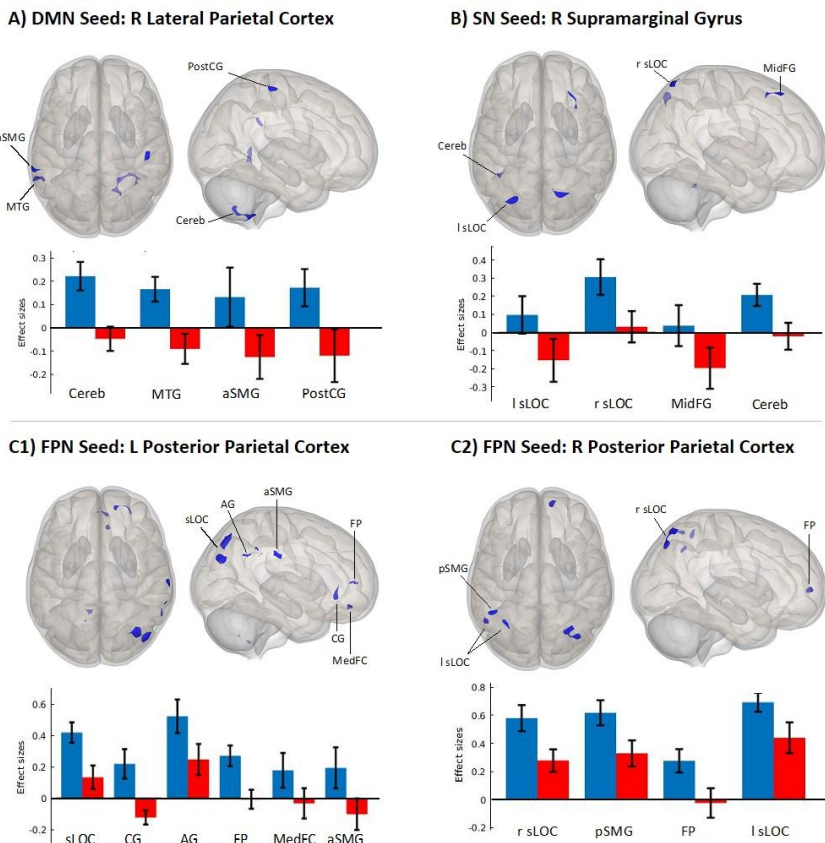
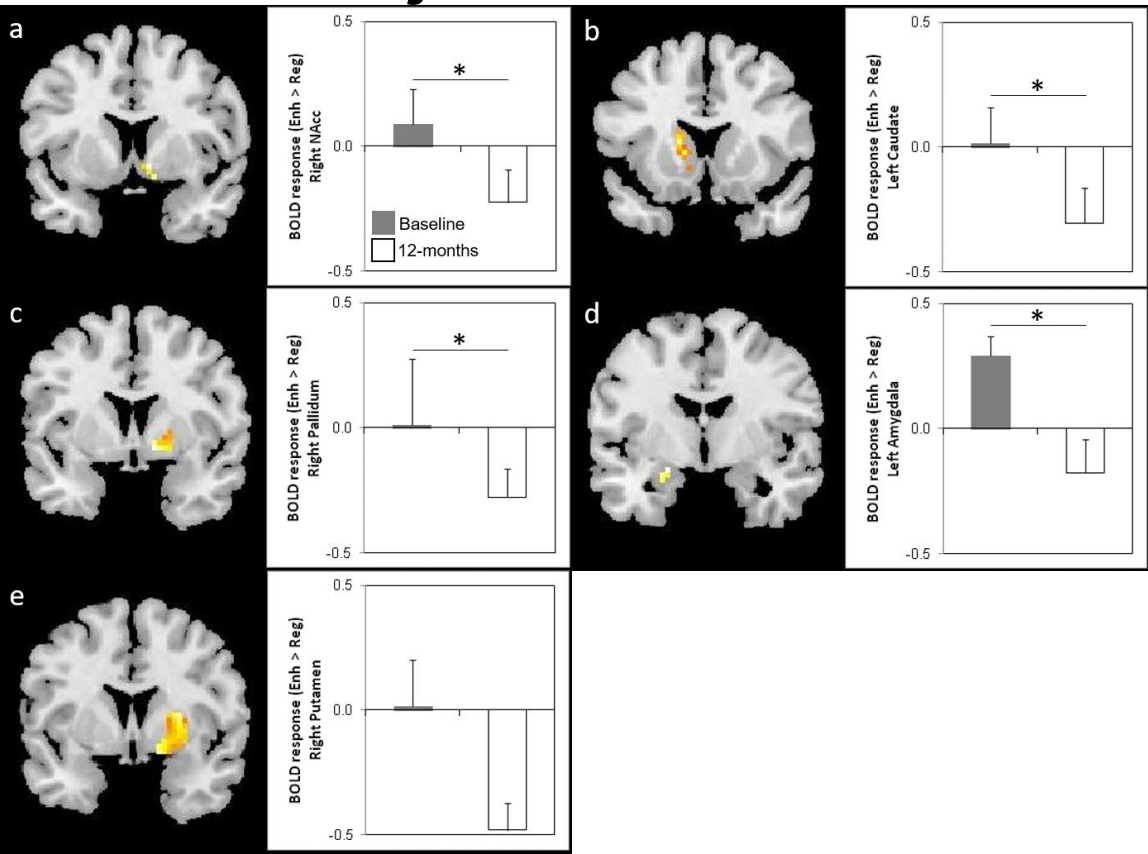




A longitudinal study incorporating a craving regulation task examined brain changes and predictors of weight loss after sleeve gastrectomy

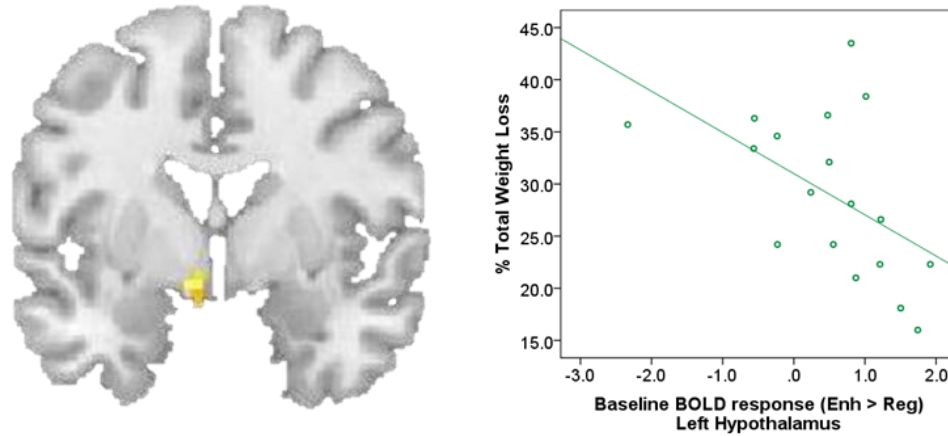


Sleeve gastrectomy reduced hedonic network activation, enhanced cognitive control activation, and changed network connectivity

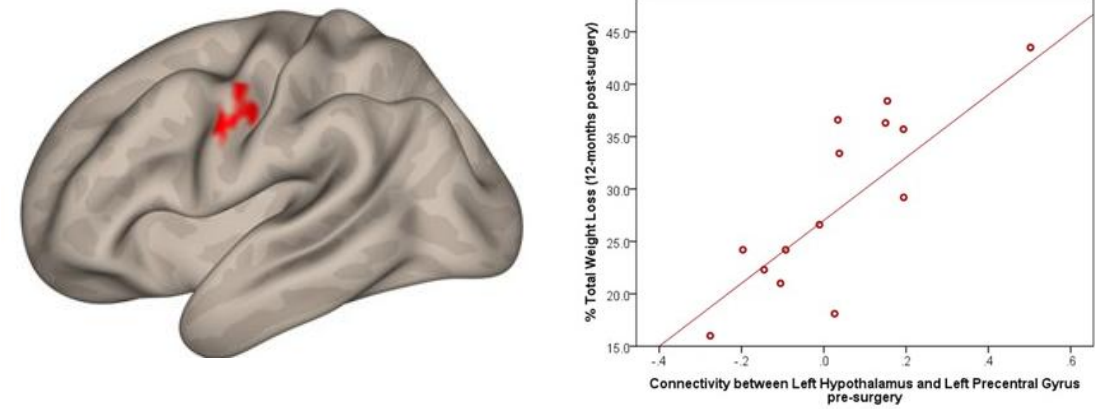


Baseline homeostatic and hedonic network activation/connectivity, but not hormones, predicted 12 months post-sleeve gastrectomy weight loss

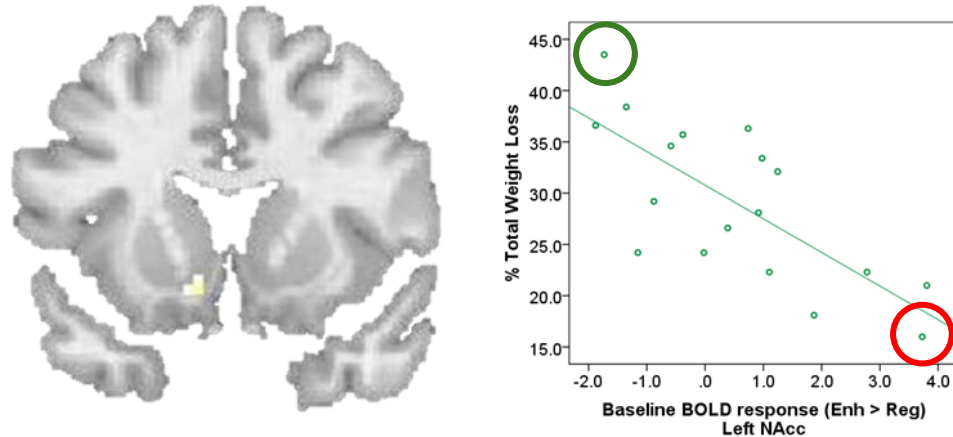
Hypothalamus activation



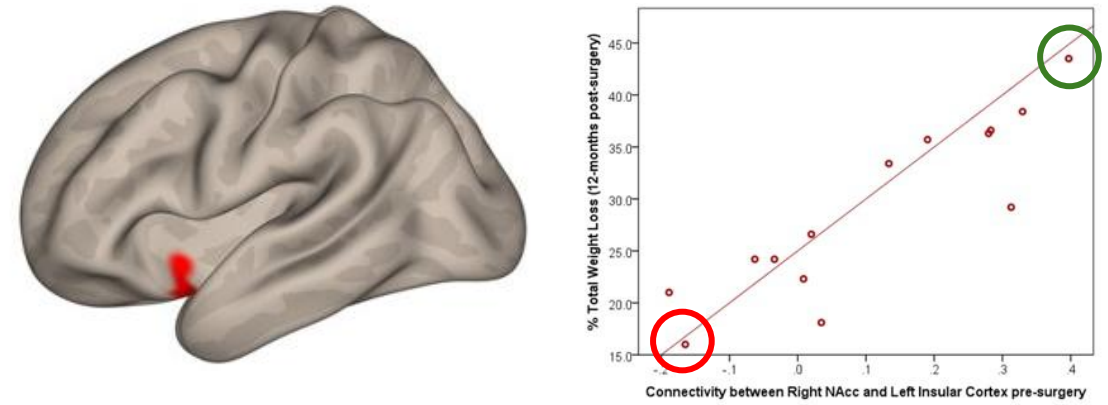
Hypothalamus-Precentral gyrus connectivity



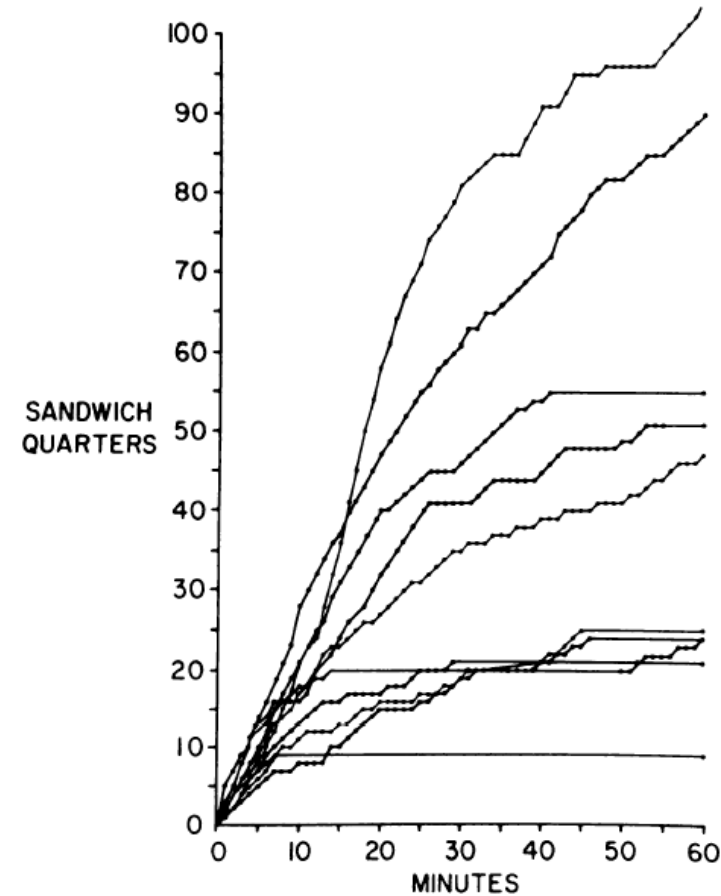
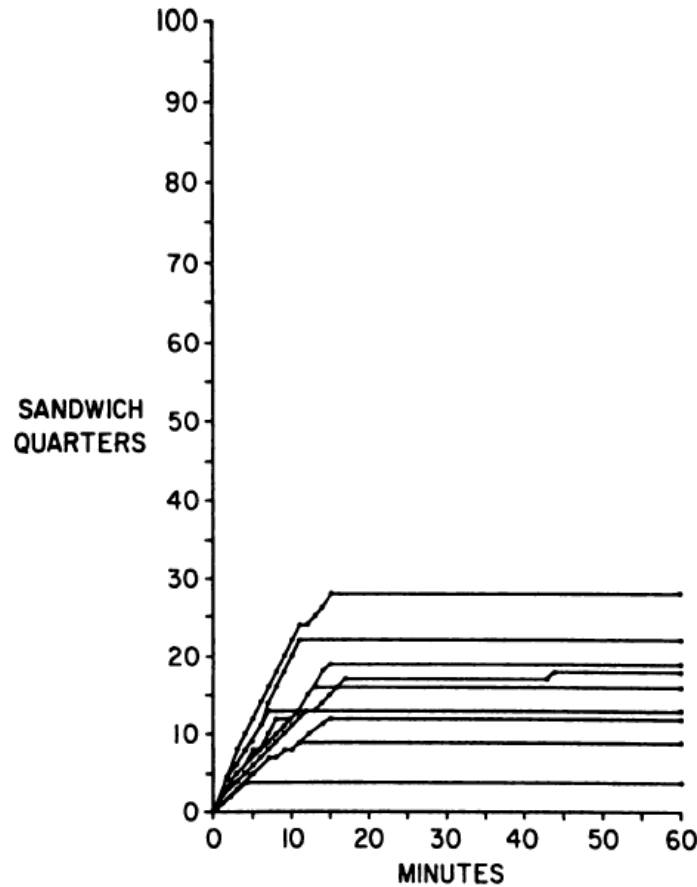
NAcc activation



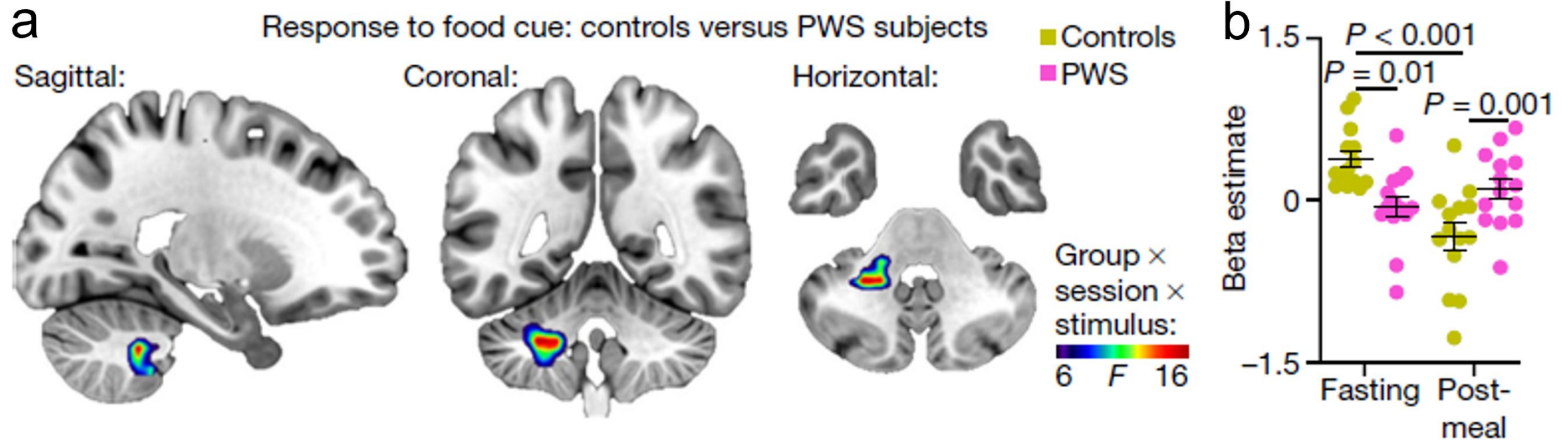
NAcc-Insular cortex connectivity



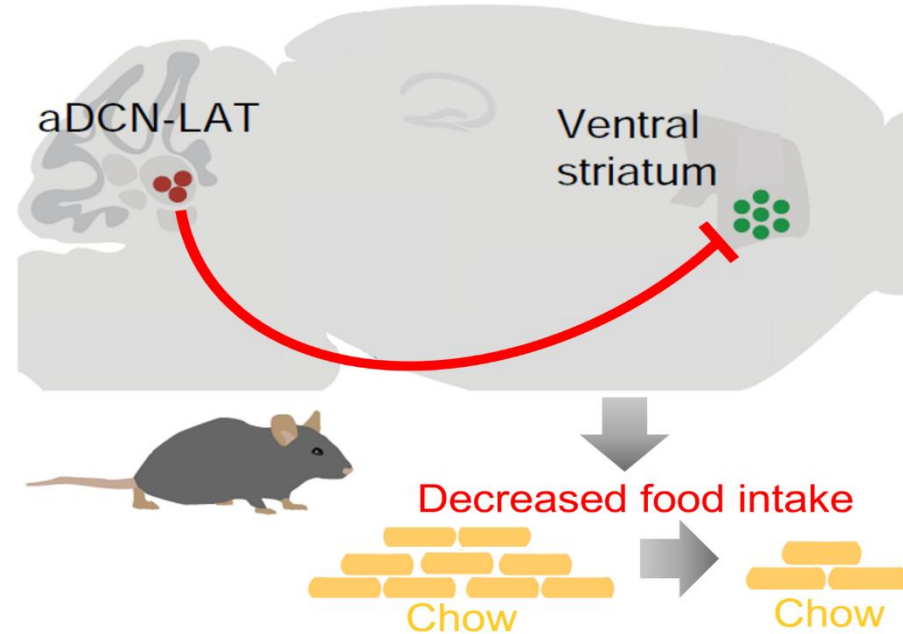
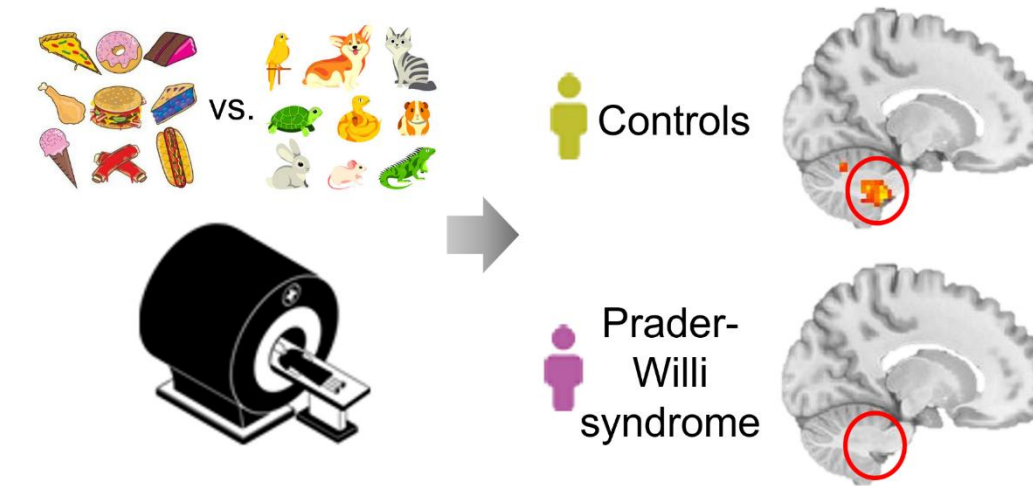
Translational collaborations allow for identification of novel appetite circuits: The case of Prader-Willi syndrome (PWS) and the cerebellum



An unbiased approach revealed differential activation to food cues in individuals with PWS, vs. BMI-matched controls, in the cerebellum



Reverse translation of findings in PWS revealed the cerebellum as a potent inhibitor of food intake

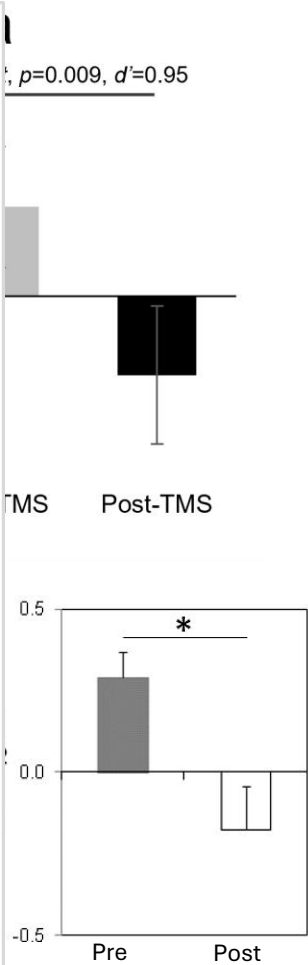
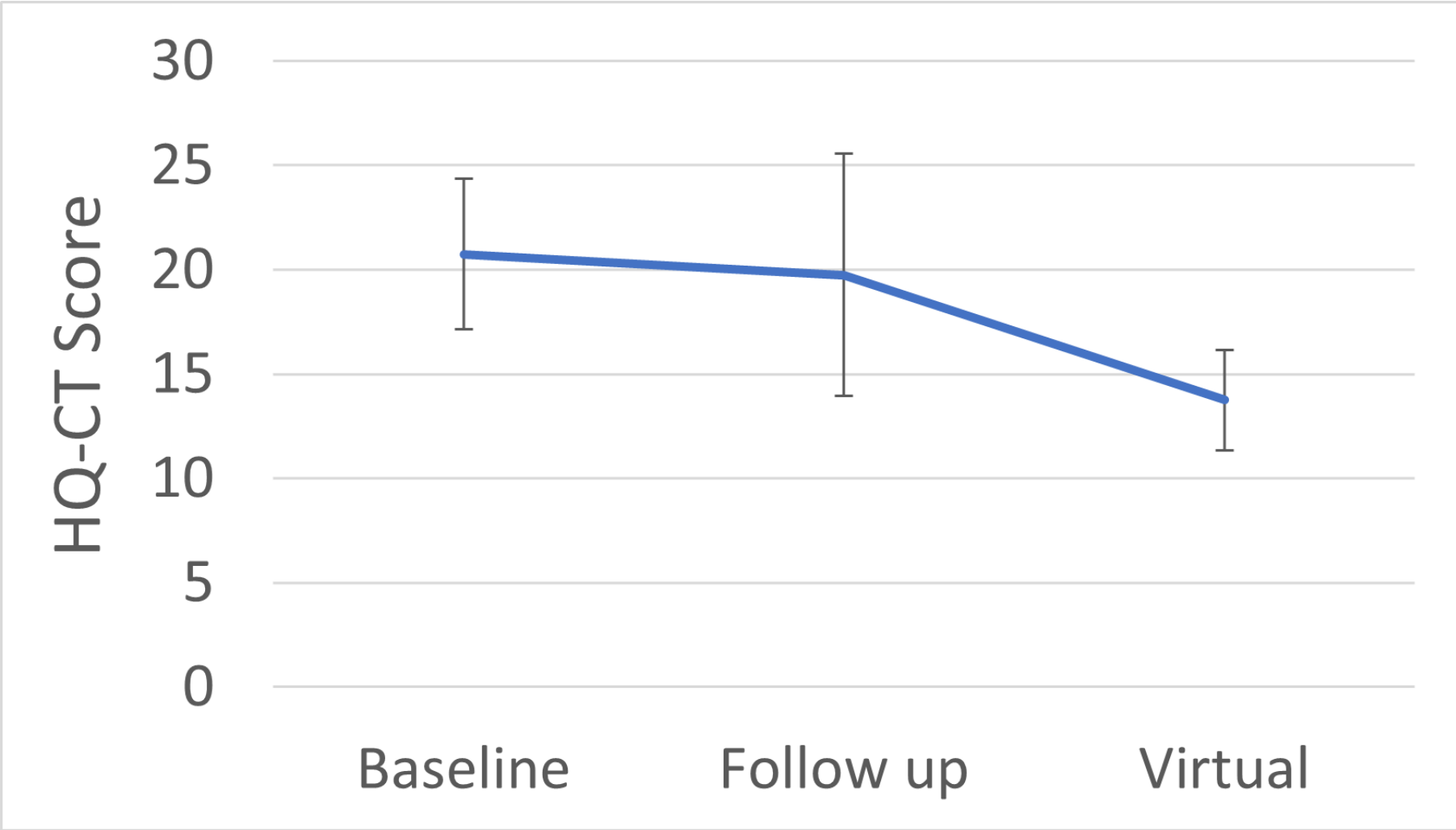
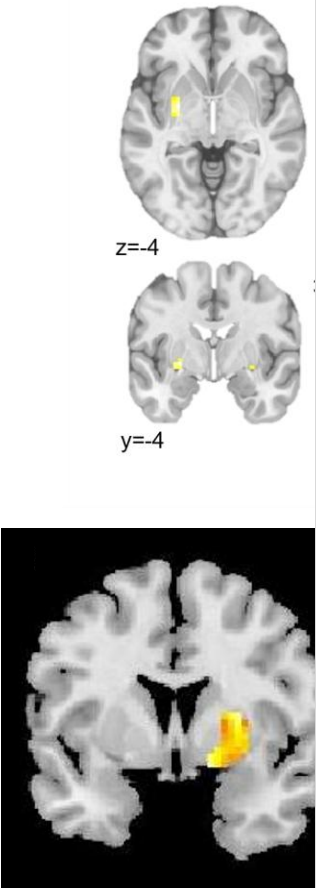


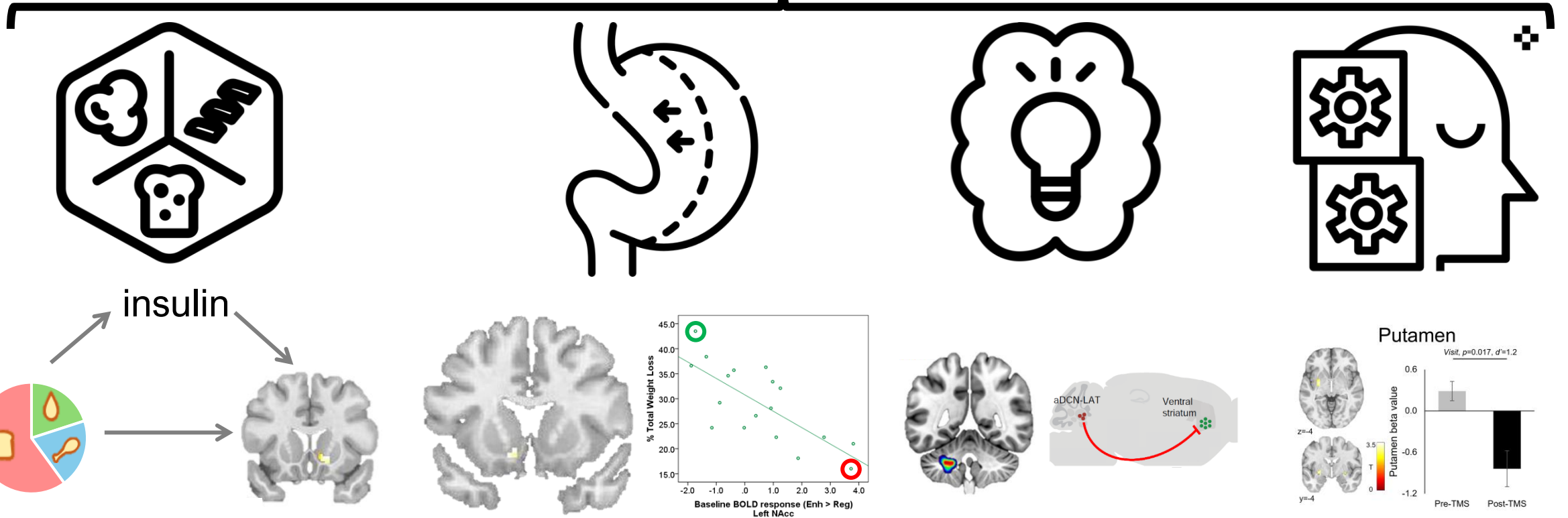
Follow-up to cerebellar-striatal satiety circuit work: Feasibility study of cerebellar TMS in PWS



Sample: 12 adults with genetically-confirmed PWS, without contraindications to TMS or MRI, and their caregivers

Follow-up to cerebellar-striatal satiety circuit work: Initial results of feasibility study of cerebellar TMS in PWS





What about the GLP-1RAs?

GLP-1 MEDICATIONS FOR WEIGHT LOSS

Semaglutide
~15%

Average Weight Loss
GLP-1 agonist

Pros

- FDA-approved for weight loss
- Proven effectiveness
- Improves blood sugar control

Tirzepatide
~20%

Average Weight Loss
GLP-1 + GIP agonist

Pros

- FDA-approved for weight loss
- More effective than semaglutide

Retatrutide
~25%

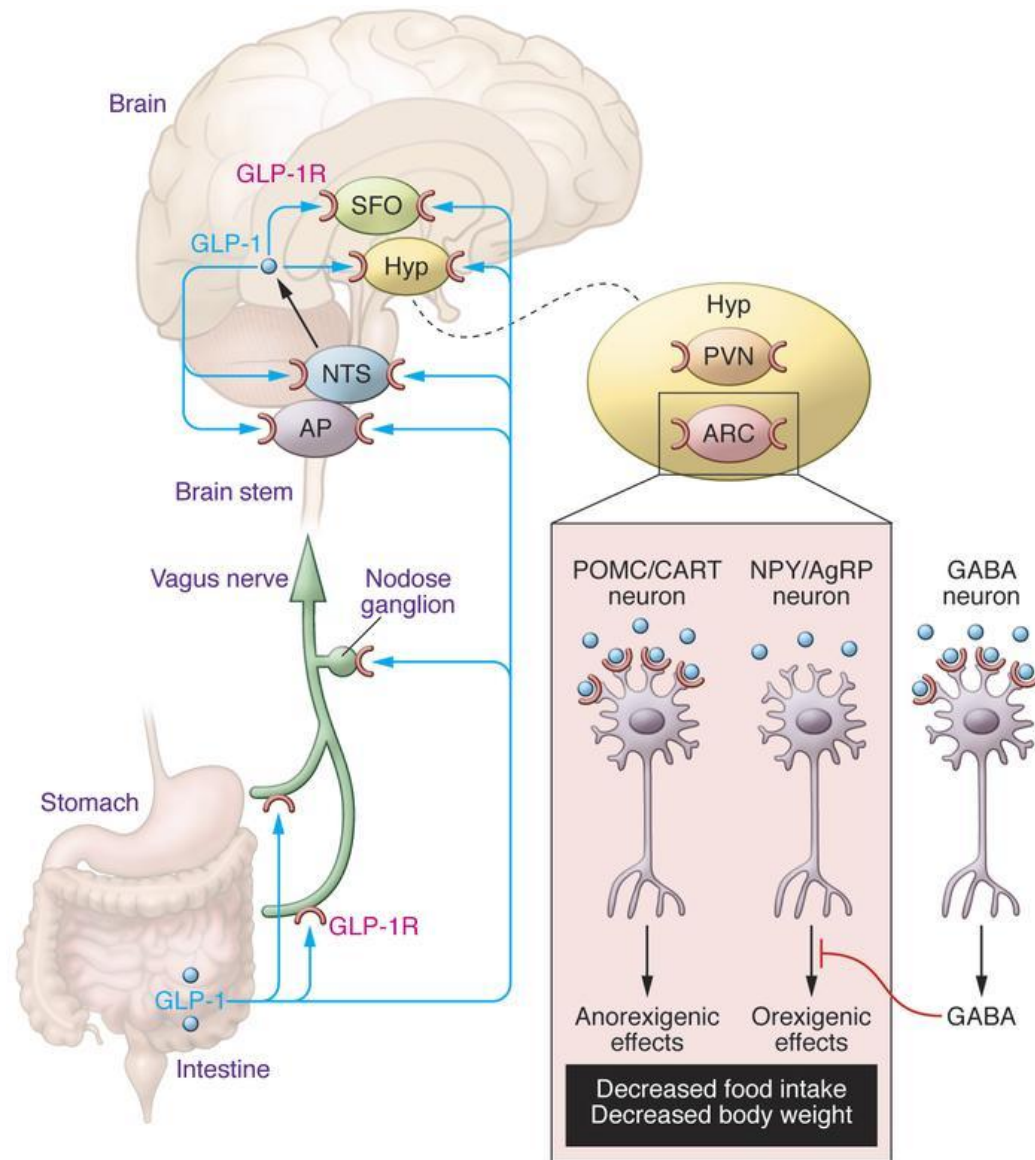
Average Weight Loss
GLP 1 + GIP +
glucagon agonist

Pros

- Most effective of the three
- Currently in clinical trials



What about the GLP-1RAs?



Glucagon-like Peptide 1 (GLP-1) Receptor Agonist Therapy and Exercise Training in People With Obesity

ClinicalTrials.gov ID ⓘ NCT07091500

Sponsor ⓘ Washington University School of Medicine

Effect of GLP1 Receptor Agonist on Brain Insulin Responsiveness

ClinicalTrials.gov ID ⓘ NCT06487832

Sponsor ⓘ University Hospital Tuebingen

Brain Plasticity and GLP-1 Receptor Agonist Treatment for Obesity (PLASTIC)

ClinicalTrials.gov ID ⓘ NCT07021937

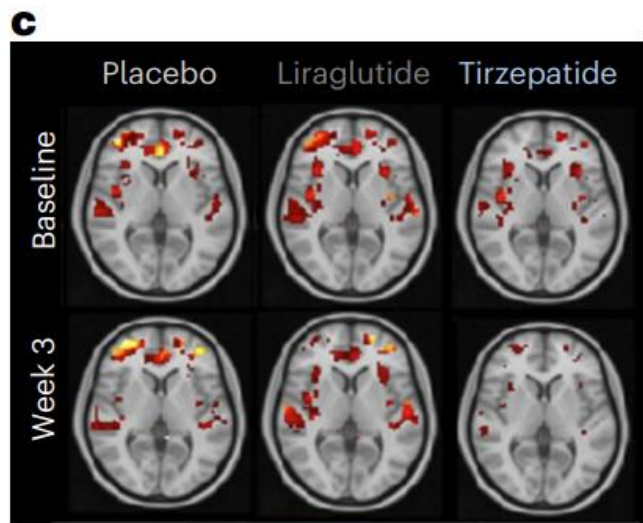
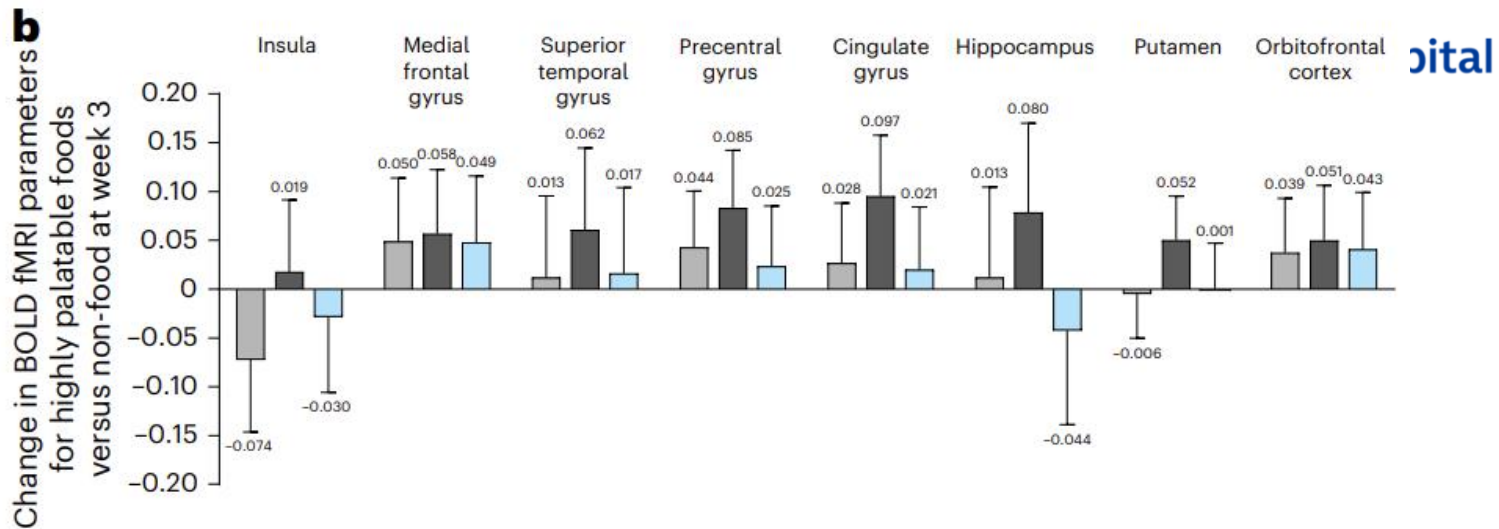
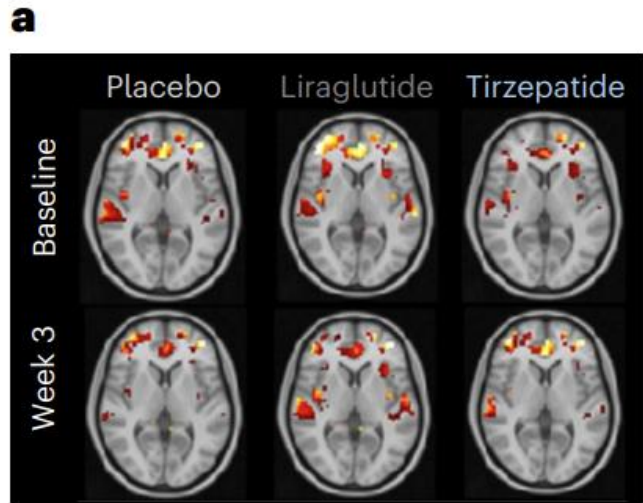
Sponsor ⓘ University of Colorado, Denver

A Study of Tirzepatide in Overweight and Very Overweight Participants

ClinicalTrials.gov ID ⓘ NCT04311411

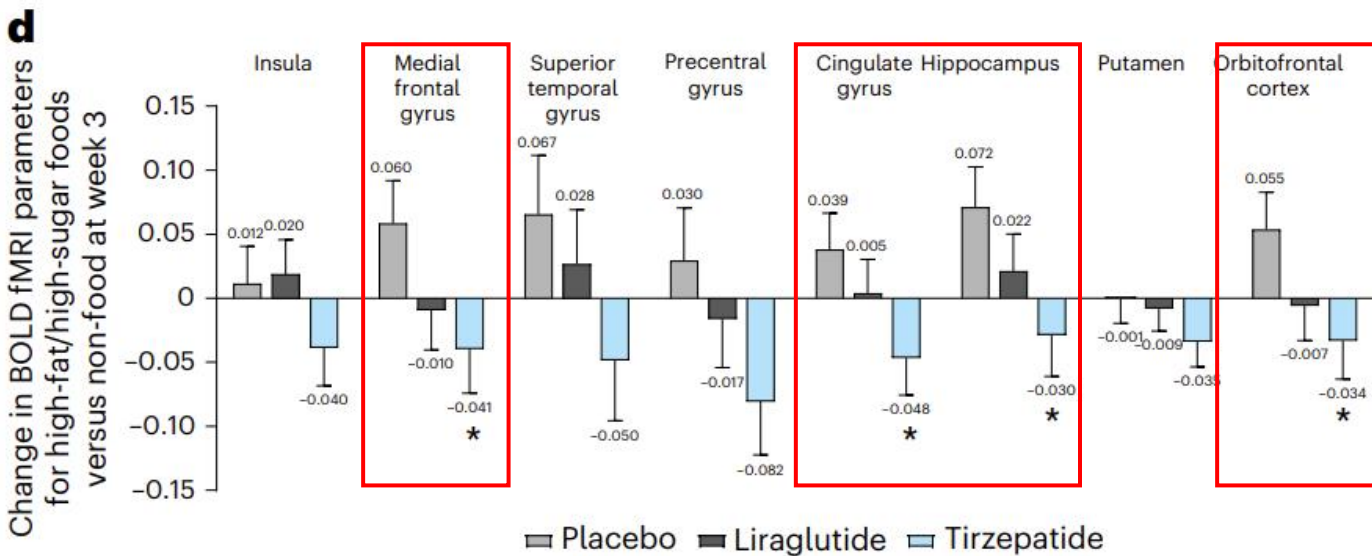
Sponsor ⓘ Eli Lilly and Company

What about the GLP-1RAs?



0 0.5

Positive color bar food > non-food



Take home messages

- Reward and homeostatic regions are sensitive to high-carbohydrate weight-loss maintenance diets.
- Dysfunction in reward and homeostatic regions resolves following bariatric surgery, and the level of function prior to surgery predicts weight loss at one year.
- Leveraging a translational collaboration identified a newly refined role for the cerebellum as a potent inhibitor of food intake.
- Non-invasive neuromodulation of the cerebellar-striatal circuit may reduce hyperphagia in a genetic form of obesity.
- Novel, highly effective GLP-1RAs may induce weight loss in part through impacts on brain reward regions.

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