Modulation of hypothalamic connectivity by food ingestion

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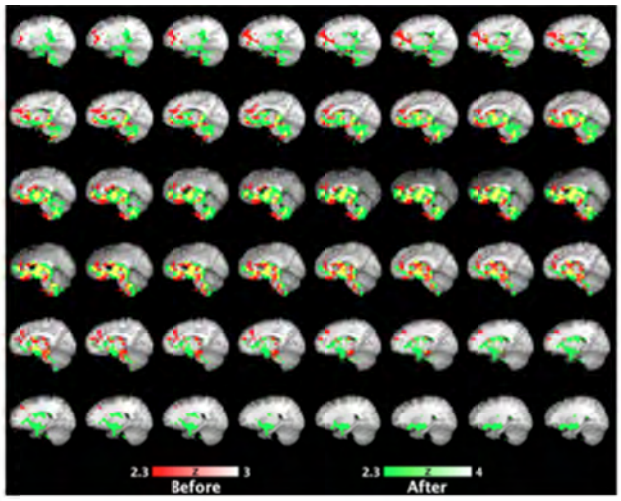
INTRODUCTION Obesity is at an epidemic proportion, affecting one-third of American adults and 17% of American children. Obesity markedly increases risk of cardiovascular diseases, such as stroke and heart diseases, cancer and diabetes regardless of race and gender. The hypothalamus (HT) plays a pivot role in the regulation of satiety and hunger. Studying hypothalamic connectivity in lean population during fasting and satiated state may help to improve our understanding of how the brain regulates hunger and satiety. In this study we utilized resting state fMRI (rsfMRI) to identify and compare hypothalamic connectivity in lean subjects during fasting and satiated state. Given that HT is located in a region of high magnetic susceptibility, the EPI parameters and shimming were carefully optimized to ensure the HT can be reliably imaged and post processing evaluation was done to ensure stable time courses in the HT.

METHODS rsfMRI were performed on seven healthy lean subjects (4 male, 3 female, 20-35 yo, BMI = 18-25 kg/m2). Subjects were instructed to fast overnight for a period of eight hours, average blood glucose of 80± 5 mg/dL. None of the subjects were on any diet program or recently lost weight. Whole-brain rsfMRI was acquired using EPI with TR = 3000ms, TE = 30 ms, and an in-plane spatial resolution of 1.7 x 1.7 mm, 5-mm sagittal slices. The total scan lasted 65 mins with an initial 10-min period of baseline pre-glucose ingestion acquisition, followed by 50 mins of post-glucose ingestion acquisition. During rsfMRI, subjects ingested standard glucola solution (75 g of glucose dissolved in 296 ml of flavored water) in a self-pace manner over 4.5 ± 0.75 min via a peroral rubber tube. Preprocessing procedure was implemented using FSL consisting of 1) motion correction 2) spatial smoothing, 3) temporal filtering between 0.01-0.08 Hz. Using the Talairach-Daemon atlas, ROI in the hypothalamus was selected. The individual timeseries of hypothalamus was used as seed to find neural structures that share similar temporal pattern that hypothalamus. The time series of 8 nuisance signals were identified for inclusion in our analyses: white matter (WM), cerebrospinal fluid (CSF), and 6 motion parameters.

RESULTS MRI protocol was optimized to ensure the HT can be reliably imaged with stable time courses. Post processing evaluation was done to ensure stable time courses in the HT. Figure 1 shows results of ROI based connectivity of hypothalamus in lean subjects in fasted and satiated state. Clusters in red represent active regions during fasting, green satiated state, and yellow common during both tasks. The major activated structures that were common and different between the fasting and satiated state are summarized in Table 1.



DISCUSSION The structures that were activated in both before and after glucose were (**Table 1**): i) The subtantia nigra plays an important role in reward and addiction and it projects to striatum (lentiform nucleus)[1]. ii) The hippocampus and anterior cingulated are part of the reward system, indicating a fulfillment of nutritional needs[2]. iii) The thalamus is activated because it receives input from sensory, visceral and gustatory systems[3]. iv) The middle and inferior frontal gyrus have been associated with decision making based on emotional and integrative control of food intake[4] and v) Caudate has been reported to be activated during food-craving episodes[5].

The structures that were engaged only during fasting were the red nucleus, inferior frontal gyrus and precuneus. Red nucleus projects to the hypothalamus[6]. Inferior frontal gyrus (BA 47) has been linked to the modulation of hunger . The output from the orbitofrontal cortex to both striatum (lentiform nucleus) and lateral hypothalamus has been reported[7]. Precuneus has been implicated during fasting state. The structures that were engaged only during satiated state were the superior temporal gyrus, posterior cingulate, fusiform gyrus, cerebellum and mid temporal gyrus. Superior temporal gyrus has been implicated in food inhibition and mid temporal gyrus has been reported to be engaged in satiation[8]. Cerebellum is believed to activate during changes in thirst/satiation state when the brain is vigilant and is monitoring its sensory systems[9]. The involvement of fusiform gyrus during satiated state contradicts previous published results. Engagement of posterior cingulated has not been reported.

Table 1. Hypothalamic connectivity

Before glucose	After glucose
Mid frontal gyrus (BA 6, BA 9)	Mid frontal gyrus (BA 9)
Thalamus	Thalamus
Lentiform nucleus	Lentiform nucleus,
Parahippocampus (BA 19, BA 36)	Parahippocampus (BA19,36,30,35,28,27)
Subtantia nigra	Subtantia nigra,
Inferior frontal gyrus (BA 20)	Inferior frontal gyrus (BA 20)
Caudate	Caudate
Red nucleus	Superior temporal gyrus
Inferior frontal gyrus	Posterior cingulate (BA 29)
Precuneus (BA 39)	Fusiform gyrus (BA 20)
-	Cerebellum.
-	Mid temporal gyrus

CONCLUSION This study optimized imaging parameters to ensure reliable detection of the hypothalamus and applied rsfMRI to identify hypothalamic network regulating hunger and satiety in healthy lean subjects. We identified some common and different activated structures before and after food ingestion, some are established and some appeared novel. Future studies will focus on validation and extending this approach to study obese subjects to undercover possible pathological neural mechanisms regulating satiety.

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