

# CLINICAL—ALIMENTARY TRACT

## Influence of Sucrose Ingestion on Brainstem and Hypothalamic Intrinsic Oscillations in Lean and Obese Women

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**BACKGROUND & AIMS:** The study of intrinsic fluctuations in the blood oxygen level-dependent signal of functional magnetic resonance imaging can provide insight into the effect of physiologic states on brain processes. In an effort to better understand the brain–gut communication induced by the absorption and metabolism of nutrients in healthy lean and obese individuals, we investigated whether ingestion of nutritive and non-nutritive sweetened beverages differentially engages the hypothalamus and brainstem vagal pathways in lean and obese women. **METHODS:** In a 2-day, double-blind crossover study, 11 lean and 11 obese healthy women underwent functional magnetic resonance imaging scans after ingestion of 2 beverages of different sucrose content, but identical sweetness. During scans, subjects rested with eyes closed. **RESULTS:** Blood oxygen level-dependent fluctuations demonstrated significantly greater power in the highest frequency band (slow-3: 0.073–0.198 Hz) after ingestion of high-sucrose compared with low-sucrose beverages in the nucleus tractus solitarius for both groups. Obese women had greater connectivity between the right lateral hypothalamus and a reward-related brain region and weaker connectivity with homeostasis and gustatory-related brain regions than lean women. **CONCLUSIONS:** In a functional magnetic resonance imaging study, we observed sucrose-related changes in oscillatory dynamics of blood oxygen level-dependent fluctuations in brainstem and hypothalamus in lean and obese women. The observed frequency changes are consistent with a rapid vagally mediated mechanism due to nutrient absorption, rather than sweet taste receptor activation. These findings provide support for altered interaction between homeostatic and reward networks in obese individuals.

**Keywords:** Resting State; Obesity; Satiety; Food Intake.

a meal with brain activity in a fasting state, or compared ingestion of a glucose solution with ingestion of water.<sup>2</sup> Although the glucose solution and water share similar oral somatosensory features and distension volume (unlike meal and fasting), the comparison of glucose and water does not allow specific statements regarding the brain's response to the absorption of nutrients in the gut. Glucose compared with water differentially activates lingual and intestinal sweet taste receptors, as well as pathways that depend on absorption and metabolism of glucose.<sup>3–6</sup>

In an effort to better understand brain–gut communication driven by the absorption and metabolism of nutrients in healthy and obese individuals, we used a paradigm involving ingestion of 2 beverages designed to be similar in sweetness but different in sucrose content. We compared ingestion of a high-sucrose beverage with a control condition of a low-sucrose beverage containing a non-nutritive sweetener to make the 2 drinks indistinguishable in terms of sweetness. These beverages should both activate sweet taste receptors but differ in vagal stimulation due to the absorption and metabolism of sucrose within the gut.

A novel aspect of this study concerns the type of functional neuroimaging and analysis performed. The dominant design of functional magnetic resonance imaging (fMRI) studies to date has involved an active task condition. For the study of food intake regulation, food images are often presented as an external cue to activate the brain. However, it is now appreciated that a wealth of information can be extracted from the fluctuations in the blood-oxygen level–dependent (BOLD) signal that are seen in the brain even when the subject is at rest and not actively engaged in discrete tasks, ushering new approaches to fMRI design and

Increased engagement of the reward-based brain networks and reduced reliance on interoceptive input has been suggested in the pathophysiology of some forms of obesity (“food addiction”).<sup>1</sup> Functional neuroimaging studies of obesity and food intake regulation have typically compared brain activity to visual food cues after ingestion of

**Abbreviations used in this paper:** BOLD, blood-oxygen level–dependent; fMRI, functional magnetic resonance imaging; HF, high frequency; LF, low frequency; MF, medium frequency; NTS, nucleus tractus solitarius; PCC, posterior cingulate cortex; PLS, partial least squares; VAS, visual analog scale.

analysis. Although several analysis approaches have been proposed to analyze changes in intrinsic brain oscillations, one approach focuses on frequency power in specific frequency bands within the range detectable in the BOLD signal thought to represent different neuronal oscillation classes.<sup>7,8</sup> Although the precise relationship between oscillatory brain dynamics and behavior remains to be established, this approach has been applied to resting-state fMRI by a growing number of researchers.<sup>9–12</sup>

By measuring sucrose-related intrinsic BOLD activity compared with a control condition of non-nutritive sweetener ingestion, we sought to monitor brain activity related to vagal stimulation triggered by various peripheral glucose-sensing mechanisms dependent on the metabolism and absorption of sugar, and to identify obesity-related changes in brain–gut communication. We used the novel tool of measuring oscillatory brain dynamics in multiple frequency bands to test 2 specific hypotheses, that ingestion of sucrose is associated with engagement of hypothalamus and brain-stem vagal pathways, as reflected in changes in specific frequency bands; and obese and lean subjects differ in their central response to sucrose ingestion. The results confirmed both hypotheses.

## Methods

### Subjects

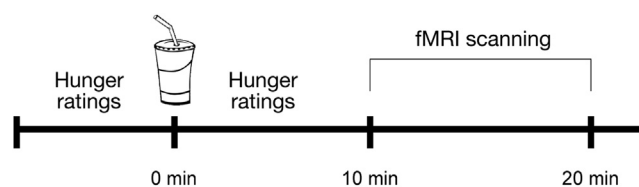
Eleven lean healthy women (body mass index 19–25) and 11 obese healthy women (body mass index 30–37) were recruited by advertisement. All subjects were right-handed. Subjects were interviewed by a nurse practitioner for absence of significant health or psychiatric conditions. Subjects diagnosed with diabetes were excluded. All subjects were regularly menstruating and were scanned 4–12 days after the first day of last menstrual period. Study protocols were performed after approval by the review committee at University of California, Los Angeles's Office of Protection for Research Subjects and informed consent was obtained from all subjects.

### Behavioral Measures

All subjects completed the Hospital Anxiety and Depression Scale, a measure of current anxiety and depression symptoms validated for nonpsychiatric samples.<sup>13</sup> Subjects also completed visual analog scales (VAS) to rate the taste of the beverages and assess hunger (How hungry do you feel?), satisfaction (How satisfied do you feel?), and desire to eat something sweet (Would you like to eat something sweet?).<sup>14</sup> Subjects were asked to make a mark across a 10-cm line representing the magnitude of their response. Qualifying statements were provided on the extreme left and right side of the 10-cm line. VAS scores were quantified by measuring the distance of the mark (in cm; range, 0–10) relative to the end of the line associated with a low/poor response; a high score reflected a high/good response for all VAS items.

### Procedures

Procedures are summarized in Figure 1. Subjects underwent 2 separate days of fMRI (1.5T) scanning. Subjects fasted, drinking only water, for 6 hours before the scan appointment.



**Figure 1.** Summary of procedures is given. On each scanning day, subjects completed hunger ratings immediately before and after beverage consumption (high or low sucrose). Commencing 10 minutes after consumption, subjects were scanned while resting for an additional 10 minutes.

Scans occurred during the morning, between 9:00 AM and 11:00 AM. Ten minutes before functional scanning, subjects consumed 296 mL of a beverage consisting of a low-calorie carbohydrate drink (Diet Ocean Spray Cranberry Juice with 50 g of Truvia; <10 calories; low sucrose) or a high-calorie carbohydrate drink (Ocean Spray Cranberry Juice with 50 g of sugar; 300 calories; high sucrose). The beverages were designed to be similar in taste and sweetness. Pilot testing in 5 healthy individuals confirmed that the drinks could not be differentiated on the basis of taste. Subjects completed the VAS questionnaires immediately before beverage consumption. Subjects consumed a different beverage on each scan day and drink order was counterbalanced with subject and investigators blinded to drink order. The beverage was presented in a nondescriptive container. Subjects drank through a straw and were fitted with a nose clip during consumption to minimize the flavor of the juice. Also, 1 oz of water was used to cleanse the palate. After beverage consumption, subjects again completed the VAS questionnaires and were encouraged to use the bathroom. Ten minutes after beverage consumption, subjects completed a 10-minute functional scan while resting with eyes closed.

### fMRI Acquisition

MRI scanning was performed using a 1.5T MRI scanner (Siemens Sonata; Siemens, Erlangen, Germany). A high-resolution structural image was acquired from each subject with a magnetization-prepared rapid gradient-echo sequence, repetition time = 2200 ms, echo time = 4.38 ms, slice thickness = 1 mm, 176 slices, 256 × 256 voxel matrices, and 1<sup>3</sup> mm voxel size. Subjects rested with eyes closed while functional BOLD images were acquired for 10 minutes in 24-slice whole brain volumes, slice thickness = 5 mm, repetition time = 2000 ms, echo time = 45 ms, flip angle = 77 degrees. After the resting scan, subjects completed additional fMRI scans involving food-related images; these data are not included in the current report, and is reported elsewhere.<sup>15</sup>

### fMRI Preprocessing

Using Data Processing Assistant for Resting-State fMRI<sup>16</sup> (<http://www.restfmri.net/forum/DPARSF>), which is based on SPM8 (Wellcome Department of Cognitive Neurology, London, UK) and Resting-State fMRI Data Analysis Toolkit,<sup>17</sup> data were slice-time and motion corrected. Nuisance covariate regression was then performed to minimize physiological noise using 6 head-motion parameters, white matter signal, and cerebral spinal fluid signal. Data were spatially normalized to the Montreal Neurological Institute template using structural scans. Spatial smoothing with a 3 mm<sup>3</sup> Gaussian kernel occurred after

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