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Resting state hypothalamic response to glucose predicts glucose-induced attenuation in the ventral striatal response to food cues

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Abstract

Feeding behavior is regulated by a complex interaction of central nervous system responses to metabolic signals that reflect nutrient availability and to food cues that trigger appetitive responses. Prior work has shown that the hypothalamus is a key brain area that senses and responds to changes in metabolic signals, and exposure to food cues induces the activation of brain areas involved in reward processing. However, it is not known how hypothalamic responses to changes in metabolic state are related to reward responses to food cues. This study aimed to understand whether changes in the hypothalamic activity in response to glucose-induced metabolic signals are linked to food-cue reactivity within brain areas involved in reward processing. We combined two neuroimaging modalities (Arterial Spin Labeling and Blood Oxygen Level Dependent) to measure glucose-induced changes in hypothalamic cerebral blood flow (CBF) and food-cue task induced changes in brain activity within reward-related regions. Twenty-five participants underwent a MRI session following glucose ingestion and a subset of twenty individuals underwent an additional water session on a separate day as a control condition (drink order randomized). Hunger was assessed before and after drink consumption. We observed that individuals who had a greater reduction in hypothalamic CBF exhibited a greater reduction in left ventral striatum food cue reactivity (Spearman's $\rho = .46$, $P = .048$) following glucose vs. water ingestion. These results are the first to use multimodal imaging to demonstrate a link between hypothalamic metabolic signaling and ventral striatal food cue reactivity.

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Keywords

appetite regulation; eating behavior; glucose; brain

Introduction

Eating behavior requires that changes in metabolic state are recognized by the central nervous system (CNS) which regulates brain responses to sensory information associated with food availability. The hypothalamus is the primary appetite control center in the brain and plays a key role in sensing and responding to changes in circulating levels of hormones and nutrients, including glucose (1). Because of its critical role in glucose sensing and energy homeostasis, investigators have used neuroimaging methods to determine how the hypothalamus responds to ingestion of a standardized glucose load (2–8). Most prior studies used Blood Oxygen Level Dependent (BOLD) functional magnetic resonance imaging (fMRI) single-slice methods focused specifically on the hypothalamic region and found a significant reduction in hypothalamic activity following glucose ingestion in normal-weight adults (2–8). Similar findings were reported in a study that used arterial spin labeling (ASL) methods and found a significant reduction in hypothalamic cerebral blood flow (CBF), a marker of neuronal activity, in response to glucose ingestion (9). These findings are also in line with earlier work using positron emission tomography (PET) showing that the ingestion of a liquid meal resulted in a decrease in hypothalamus CBF (10–12).

In our current environment with abundant exposure to highly palatable foods, hedonic processes mediated by dopaminergic brain pathways play a key role in promoting feeding behavior (13). fMRI task based food-cue paradigms are commonly used to target hedonic aspects of feeding behavior, and prior studies have implemented these procedures to identify how hunger modulates neural food-cue reactivity (see meta-analysis (14)). Results indicate that when compared to a fasted state, a satiated state is associated with diminished brain responses to food cues in regions previously implicated in processing sensory food cues including the ventral striatum, orbital frontal cortex (OFC), amygdala, insula, and hypothalamus (15–25). More recently, fMRI studies have also reported that brain reactivity to food cues in areas involved in appetite and reward processing is modulated by glucose ingestion (26,27). Together, prior work has suggested that changes in metabolic state can modulate brain reward sensitivity to food cues.

However, fMRI has not previously been used to investigate the interaction between metabolic state-dependent shifts in hypothalamus activity and task-induced brain activation to food cues within brain areas implicated in food reward. We combined two neuroimaging modalities, ASL and BOLD-fMRI, and leveraged the unique advantages of both techniques to study how glucose-induced changes in hypothalamic activity are related to changes in food-cue reactivity within brain reward areas.

To determine the hypothalamic response to glucose-induced metabolic signals, we used ASL, which provides a semi-quantitative cerebral blood flow (CBF) measurement expressed in physiological units (mL/100 g brain tissue/min) and can capture low frequency changes in brain activity (28,29). We used BOLD-fMRI (30) to detect task-dependent neural changes to

pictures of food and non-food items (as a control). BOLD effects are measured using rapid volumetric acquisition of T_2^* weighted images(31). Neuronal activation (in response to seeing a picture of chocolate cake, for example) leads to an increase in local CBF and a reduction in local deoxyhemoglobin, which causes an increase in BOLD T_2^* signal. While BOLD has advantages over ASL for examining task-induced neural activation and has better spatial resolution, this method assesses only relative changes in BOLD signal in specific brain regions, and does not measure baseline differences in metabolic state. In this study, we combined ASL to measure state-dependent changes in hypothalamus CBF and BOLD-fMRI to assess food cue reactivity within reward-related brain regions to investigate the link between glucose-induced changes in the hypothalamic CBF and food cue reactivity in reward-related regions.

Given prior evidence suggesting that changes in metabolic state can modulate brain reward sensitivity to food cues (15-25), we predicted that glucose-induced reductions in hypothalamic activity would correlate with reductions in food-cue reactivity within brain areas implicated in reward processing.

Methods

Participants

Twenty-five healthy individuals (12 male, 13 female) between the ages of 19 ~ 25 years old with a body mass index between 19 ~ 45 kg/m² participated in this study. Participants gave written informed consent, and all experimental procedures were approved by the Institutional Review Board of the University of Southern California (USC). Participants did not have any history of eating disorders, diabetes or other medical illnesses. Also they were nonsmokers and were not on weight-loss diets or taking medications (with the exception of oral contraceptives). Participants were all right-handed and had normal or corrected to normal vision. Participants were asked to maintain their typical diet and physical activity levels throughout this study, and female participants were studied during the follicular phase of their menstrual cycle.

Overview of Study Design (Figure 1)

Anthropometric data were collected during a screening visit. Magnetic resonance imaging (MRI) visits were performed in the morning between 9:00 to 11:00 a.m. after a 12-hour overnight fast at the Dana & David Dornsife Cognitive Neuroscience Imaging Center at USC. Pulsed arterial spin labeling (PASL) was performed to determine hypothalamic CBF in the fasted state and again between 10 and 20 minutes and 30 and 40 minutes after the ingestion of glucose (75 grams in 300mL water). Participants were required to finish drinking within 2 minutes. The food cue task (details below) was performed between 20 and 30-minute after ingestion of the study drink. Hunger ratings were collected in the fasted state and again at ~10-minute and ~30-minute after drink. A water (300 mL) drink session was conducted as a control in a subset of twenty participants on a separate day, and drink order was randomized and blinded. Non-sweetened cherry flavoring was added to both the glucose and water study drinks to improve palatability. The timing for PASL, food cue task and appetite ratings during a water drink session were consistent with the glucose session.

Participants' body weight and 24-hour dietary data were collected at each study session. This study is part of a larger ongoing project examining brain responses to different types of sugar.

Anthropometric and dietary data measurements

Height was measured to the nearest 0.1 cm using a portable stadiometer and weight to the nearest 0.1 kg using a portable scale. 24-hour dietary recalls were collected using the multi-pass interview technique (32) by trained study personnel and analyzed using Nutrition Data System for Research (33). Total caloric intake (kcal) for the 24-hours prior to the study visits and body weight (kg) on the morning of the visits were submitted for paired-t tests to assess for differences between sessions.

Hunger Scale

Hunger was rated from 1 to 10 preceded by the question, “how hungry do you feel right now”, and anchored by “I am not hungry at all” on the left and “I have never been more hungry” on the right. Hunger rating was administered at baseline, +10 and +30 min after drink. Change in hunger rating was calculated as subtracting mean hunger score after drink from baseline, and submitted for a paired-t test for a comparison of glucose and water effects on hunger.

Food Cue Task

In the MRI scanner participants completed the food cue task. In this randomized block design, participants were presented with a total of 12 food cues and non-food cues visual activation blocks using Matlab (The MathWorks, Inc., Natick, Massachusetts, United States) and Psychtoolbox on a Mac laptop. There were 4 photographs presented in a random order in each block, and each photograph was presented for 4 seconds with 1 second waiting time between photographs. No picture was presented for more than once. Food cues consisted of high-calorie, palatable food items such as cookies, french fries, and hamburgers. The control stimuli consisted of non-food neutral pictures such as books and baskets. Pictures were previously matched for visual appeal (34–36). The duration for this food cue task was ~9 minutes.

MRI Imaging Parameters

Imaging data were collected using MAGNETOM Prisma^{fit} MRI scanner. Participants laid supine on a scanner bed, viewing stimuli through a mirror mounted over the head coil.

Pulsed arterial spin labeling (PASL)

ASL MRI is a non-invasive method for the quantification of perfusion. PASL magnetically tags the arterial blood before entering the brain and then examines the transit time for the tagged blood to reach specific tissues, thereby providing a direct measure of cerebral blood flow (28,29). ASL data were acquired with a PASL sequence using the QUIPSS-II method (37,38). In addition, the “proximal inversion with a control for off-resonance effects” (PICORE) mode was employed in order to provide high labeling efficiency (39). A total of 120 interleaved label and control volumes were acquired along with one M0 image with

following parameters: field of view (FOV)= 192 mm, matrix = 64×64 , bandwidth= 2232 Hz/Pixel, slice thickness=5 mm, interslice spacing= 0 mm, Repetition time (TR)= 4000 ms, echo time (TE)= 30 ms, flip angle=90°, TI1/TIs/TI2 = 700/1,800/1,800 ms, label duration=1675 ms, slab thickness=100mm, in-plane resolution = $3 \times 3 \text{ mm}^2$. The timing of the inversion pulses (TI) was optimized to reduce intravascular signal intensity at 3 T (40). The duration of the PASL acquisition was 8 minutes and 18 seconds.

BOLD-fMRI

Functional scans were acquired with a single-shot gradient echo planar imaging (EPI) sequence. Thirty-two 4 mm thick slices that cover the whole brain will be acquired using the following parameters: TR=2,000 msec, TE=25 msec, bandwidth=2520 Hz/pixel, flip angle=85°, FOV = 220×220 mm, matrix=64×64. A high resolution 3D Magnetization Prepared Rapid Gradient Echo (MPRAGE) sequence (TR=2530 ms; TE=2.62 ms; bandwidth=240 Hz/pixel; flip angle= 9°; slice thickness=1 mm; FOV=256×256 mm; matrix=256 × 256) was used to acquire structural images for multi-subject registration.

ASL analysis

We used Bayesian Inference for Arterial Spin Labeling (BASIL) toolbox to determine regional cerebral blood flow within the hypothalamus. The bilateral hypothalamus region of interest (ROI) was defined by drawing a 2-mm-radius around the peak voxel reported in Page et al., 2011 (34) where the hypothalamus showed a significant response to changes in circulating glucose levels during a food cue task. The hypothalamus ROI is included in the Supplemental Material. ASL data were first motion corrected then tagged and untagged images were subtracted to obtain perfusion-weighted images. PASL volumes were registered to the individual participant's T_1 -weighted high-resolution anatomical volume using an affine registration with 12 degrees of freedom. The hypothalamus ROI in standard MNI space was inverse transformed to each individual's T_1 -weighted image. Visual inspection was performed in each individual's hypothalamus ROI and the ROI was manually edited to ensure it was constrained within the hypothalamus. Regional CBF in the hypothalamus was calculated in the baseline prior to a drink, and again at 10-20 minute and 30-40 minute after a drink. Correlation between baseline hypothalamic CBF on a glucose day and water day was performed to examine test and retest reliability of CBF data. Post vs. preglucose differences on the hypothalamic CBF were compared at each time point using paired-t tests. The same analysis approach was performed for water session data in order to examine whether there were any changes in the hypothalamic CBF following a water drink. Repeated measures of ANOVA with two within-subject factors drink (glucose or water) and time point (10-20 minutes or 30-40 minutes) were conducted on CBF change from baseline, and paired-t tests were performed to compare glucose and water on CBF change from baseline at each time point. ANOVA results were included in the supplemental material.

fMRI Analysis

We used fMRI Expert Analysis Tool version 6.00, part of the Oxford University Centre for Functional MRI of the Brain Software Library (<http://www.fmrib.ox.ac.uk/fsl>) to process fMRI data. Four functional volumes (4 TRs) acquired at the beginning of each MRI session

were discarded in order to account for magnetic saturation effects. One participant's glucose session (lean, male) was excluded from food cue imaging data analysis due to an acquisition error. fMRI preprocessing steps included motion correction, high-pass filtering (100 s) and spatial smoothing with a Gaussian kernel of full-width at half-maximum=5mm. The functional data were first mapped to each participant's anatomical image, and then registered into standard space [Montreal Neurological Institute (MNI)] using affine transformation with FLIRT(41) to the avg152 T₁ MNI template. Food and non-food events were added to the General Linear Model (GLM) after convolution with a canonical hemodynamic response function. Temporal derivatives and temporal filtering were added to increase statistical sensitivity. Locations for ROI analyses were selected based on a meta-analysis of brain regions implicated in feeding behavior that have been consistently shown to be responsive to visual food cues and included: left orbital frontal cortex (OFC), left ventral striatum (VS), left amygdala, left hippocampus, bilateral anterior insula, bilateral middle insula, bilateral precuneus, and left postcentral gyrus (42). The same regions were used in our previous study as ROIs (24). Eight ROIs (left OFC, left ventral striatum, left amygdala, left hippocampus, bilateral anterior insula, bilateral middle insula, bilateral precuneus, and left postcentral gyrus) were defined by drawing a 4-mm-radius sphere around the peak voxel reported in the meta-analysis of food cue reactivity studies (42). For the ventral striatum, a 2-mm-radius sphere was drawn because of its smaller size. Individual percent signal change was calculated for food vs. non-food contrast in each ROI (averaged over all voxels within each ROI), and for each drink and each subject. It is important to keep in mind that the ROIs are based on meta-analysis of food-cue reactivity studies, and thus it is likely that the signal differential (food vs. nonfood) represents a difference between activations rather than deactivations, although these data do not directly distinguish these possibilities. Unlike PASL acquisitions, which were conducted both before and after drink ingestion, the food cue task was performed only after drink ingestion (separately for water and glucose consumption sessions). In order to calculate change in the food cue reactivity following glucose, we subtracted food cue reactivity on the glucose session from food cue reactivity on the water session. In this case, food cue reactivity on a water session was used as a baseline condition. Paired-t tests were conducted to compare glucose and water differences on food cue reactivity in each ROI. The purpose of this analysis was to identify regions that respond differently to food cues after glucose vs. water ingestion, and any such regions were then used for correlation analyses to determine the relationship between the change in hypothalamic CBF response to glucose and the change in food cue reactivity after glucose ingestion. In addition, whole-brain analysis was conducted to measure glucose vs. water differences on food cue reactivity (FDR cluster corrected for multiple comparisons, $Z > 2.3$, $P < .05$). The difference in hypothalamic CBF after glucose relative to water was used as a covariate to predict glucose vs. water differences on food cue reactivity throughout the whole brain.

Statistical Analysis

The primary interest was to examine the correlation between glucose-induced changes in the hypothalamic CBF measured by ASL and food cue reactivity measured by BOLD-fMRI. Our 2-step approach was to: (1) identify the time point(s) and the region(s) that were most impacted by glucose ingestion; (2) to perform correlation analyses between hypothalamus

CBF and food cue reactivity findings on the time point(s) and region(s) that were responsive to glucose ingestion. It is important to note that since many comparisons were made, uncorrected test-statistics from step 1 are not a valid basis for significance testing. Non-parametric Spearman correlation analyses were used to examine relationships between 1) change in the hypothalamic CBF (glucose vs. water ingestion or post vs. pre-glucose ingestion) and food cue reactivity after glucose vs. water ingestion (limited to regions which showed main effect of drink), and 2) change in the hypothalamic CBF and change in the hunger rating following glucose vs. water ingestion. We explored relationships between demographics (e.g., age, BMI, sex) and glucose-induced changes in resting state CBF, food cue reactivity and hunger using Spearman correlation method for continuous variables and Wilcoxon–Mann–Whitney tests for categorical variables. Given this small sample size, the correlations based on participant characteristics are underpowered to detect moderate effects thus included only for descriptive purposes. All statistical analyses were performed using SPSS (IBM SPSS Statistics for Mac, Version 19.0. Armonk, NY: IBM Corp) and a value of $P < 0.05$ was considered significant.

Results

We observed the maximum decrease in the hypothalamic CBF between 10 and 20 minutes post-glucose drink compared to baseline ($t_{(1,24)} = -2.094$, $P = .047$, Figure 2). Change in the hypothalamic CBF response to glucose between 30 and 40 minutes was not significantly different from baseline. Of note, there was no change in the hypothalamic CBF after water ingestion ($t_{(1,19)} = -.12$, $P = .91$, see Figure 2). Although the main effect of drink from 2×2 ANOVA was not significant, exploratory analysis suggested there was a trend in glucose vs. water difference on change in the hypothalamic CBF between 10 and 20 minutes post drink vs. baseline ($t_{(1,19)} = -1.947$, unadjusted $P = .067$, adjusted $P = .13$). Glucose relative to water ingestion was associated with reduced hunger ratings ($t_{(1,19)} = -2.19$, $P = .041$). The hypothalamic CBF data correlation coefficient for test and retest reliability was $r = .54$ ($P = 0.013$).

Based on the 95% confidence interval of glucose vs. water on food cue reactivity in each ROI (Figure 3), left VS showed the greatest reduction of food cue reactivity following glucose vs. water ingestion among ROIs and was selected for subsequent correlation analysis. Exploratory whole-brain analysis suggested that following glucose vs. water ingestion, the bilateral OFC and VS showed significantly decreased food cue reactivity (Supplemental Material Figure 2 and Table 2). Change in the hypothalamic CBF after glucose vs. water was not significantly correlated with whole-brain food cue reactivity following glucose vs. water ingestion.

There was a positive correlation between change in the hypothalamic CBF response to glucose vs. water and BOLD signal change in left ventral striatum response to food cues following glucose vs. water (Spearman's $\rho = .46$, $P = .048$, Figure 4). The significant change in the hypothalamic CBF response to glucose at 10-20 minutes vs. baseline was also positively correlated with change in left ventral striatum food cue reactivity following glucose vs. water (Spearman's $\rho = .456$, $P = .0497$), and positively associated with change in subjective ratings of hunger after glucose vs. water (Spearman's $\rho = .724$, $P = .0003$).

Participants' body weight (Mean difference $\pm$ SEM: 1.34 $\pm$ 1.20 kg, $P=.27$) and total energy intake (234.31 $\pm$ 143.43 kcal, $P=.11$) were not significantly different between glucose and water sessions. We did not observe significant relationships between age, sex, or BMI and brain or hunger responses to glucose vs. water ingestion.

Discussion

Identifying how our brain integrates information about metabolic signals and environmental food cues is critical in our efforts to understand neurobehavioral regulation of food intake and obesity risk. Neuroimaging studies have provided important insights into neural correlates of eating behavior and the modulating effects of hunger state on brain activity. In earlier studies, investigators used PET to examine regional CBF in a state of hunger (after a prolonged fast) and a state of satiation (after a liquid meal) (10–12,43). In normal-weight adults, hunger was associated with greater CBF in the hypothalamus and other limbic areas whereas satiation was associated with increased CBF in the prefrontal cortex (10). These studies provided the framework for the use of neuroimaging techniques to identify how metabolic state influences brain systems involved in the regulation of feeding in humans.

In the current study, we combined the strengths of two neuroimaging modalities ASL and BOLD-fMRI to examine whether glucose-induced shifts in hypothalamic activity would be associated with brain responses to food cues within brain areas involved in reward processing. We observed that greater reductions in hypothalamus CBF in response to glucose ingestion correlated with diminished responses to food cues in the left ventral striatum and reduced ratings of hunger.

Prior studies have consistently shown a significant reduction in hypothalamic activity in response to the ingestion of glucose in normal-weight adults (2-8), and this hypothalamic response has been suggested as a biomarker of satiety signaling (4,9). Our study is consistent with this proposal and showed that the reduction in hypothalamic response to glucose ingestion was positively associated with reductions in subjective ratings of hunger. In keeping with prior reports (2,3,9), we observed the maximum hypothalamus response was around 10 to 20-minute post glucose ingestion. We observed that the hypothalamic activity returned towards baseline by about 30 to 40-minute post-glucose ingestion, which is consistent with some reports(2,3), whereas others(4-9) have reported a more prolonged reduction in the hypothalamic activity following oral glucose. The mean hypothalamic CBF in the current study was lower than what was reported in Page et al., 2013. We speculate that differences in the demographics of study participants as well as differences in MRI scanners and acquisition methods may contribute to these discrepancies. While the length of time that hypothalamic activity is reduced following glucose ingestion is not yet resolved, our findings support prior work showing a significant reduction in hypothalamic activity following glucose ingestion and provide support for its role as a central marker of glucose-linked signaling.

In recent years, researchers began exploring how metabolic states impact CNS response to sensory food cues. For example, functional neuroimaging studies indicated that a satiated vs. fed state was associated with diminished brain responses to external food cues (15–25) in

regions previously implicated in processing sensory food cues including the ventral striatum, OFC, amygdala, insula, and hypothalamus. These studies suggest that metabolic state may modulate brain appetitive responses to food cues. However, pure metabolic signals (independent from food cue reactivity) in the hypothalamus were not measured in these studies, thus a link between shifts in hypothalamic activity in different metabolic states and food cue reactivity could not be directly tested. In this study, using two functional imaging modalities (ASL and BOLD) allowed us to independently measure glucose-induced changes in hypothalamic CBF and food cue reactivity in order to test the interaction of CNS metabolic signaling and neural food cue reactivity. Our data indicate that the hypothalamic response to glucose ingestion is linked to the glucose-induced attenuation in the ventral striatum response to food cues. The ventral striatum is consistently implicated in reward processing (44), particularly signaling motivational property of rewards (45). The hypothalamus has functional connections with the ventral striatum (46), and prior studies observed that metabolic state influences the ventral striatum response to food cues (16,20,47). Additionally, satiety hormones essential for feeding behavior, including insulin (26,48) and leptin (16), have shown modulatory effects on the ventral striatal response to sensory food cues. Together with prior results, the link between hypothalamus CBF and ventral striatum food cue reactivity following glucose vs. water ingestion suggests an interaction between changes in metabolic state and motivation for food.

The relatively small sample size is a limitation of this current study. Given the small sample size we were not able to directly test for sex, age or adiposity related differences in brain and hunger responses to glucose ingestion. Although self-reported hunger and anticipatory responses to receipt of food rewards are in close proximity of actual food intake, it would be of interest to examine if hypothalamic signal also predicts real food consumption in future studies.

In conclusion, theoretical frameworks have been proposed to investigate the interactions of metabolic signaling and brain reactivity to food-related cues (49–51). Leveraging the strengths of ASL and BOLD modalities in neuroimaging studies of feeding behavior may allow an improved approach for studying the interactions between hypothalamic responses to metabolic signals and food-cue reactivity in reward-related regions. This combined approach could help identify links between state-dependent changes and cue-dependent changes. For example, in the appetite field, this approach could be used to address questions related to how neural responses to caloric restriction are related to reactivity to brain response to healthy vs. unhealthy food cues. And this approach could also open new doors for future neuroimaging studies to examine obesity-related effects on the interactions between metabolic signaling and food-cue reactivity that are integral to the neurobehavioral regulation of food intake.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Overview of Study Sessions. Pulsed arterial spin labeling was performed to determine hypothalamic cerebral blood flow (CBF) in the fasted state and again between 10 and 20 minutes and 30 and 40 minutes after the ingestion of glucose or water. The food cue task (FCT) was performed between 20 and 30-minute after ingestion of the study drink. Time points after drink reflect **the middle** of CBF measurements, which started after the completion of drinking and at the start of the MRI acquisitions (which continued for approximately 8 to 9 minutes). Participants were required to finish drinking within 2 minutes.

Figure 2.

Hypothalamic cerebral blood flow (CBF) response to ingestion of glucose (N=25) or water (N=20). The maximum decrease in the hypothalamic CBF was observed between 10 and 20 minutes post-glucose drink compared to baseline ($P=.047$). Time points after drink reflect the **middle of** CBF measurements, which started after the completion of drinking and at the start of the ASL acquisition, which continued for approximately 8 minutes.

Figure 3.

95% confidence interval of glucose vs. water on food cue reactivity in each region of interest (N=19). Y axis: 95% confidence interval of percent signal change on food cue reactivity following glucose vs. water. X axis: region of interest. L: left.

Figure 4.

Correlation between glucose-induced changes in the hypothalamic CBF and ventral striatal food cue reactivity. Individuals with a greater reduction (10-minute vs. baseline) in hypothalamic CBF response to glucose (vs. water) were less responsive to food cues in the ventral striatum after glucose vs. water (Spearman's $\rho = .46$, $P = .048$).