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Effective connectivity of a reward network in obese women

Luke E. Stoeckel[1,2], **Jieun Kim**[3], **Rosalyn E. Weller**[1], **James E. Cox**[1], **Edwin W. Cook III**[1], and **Barry Horwitz**[3]

[1]Department of Psychology, University of Alabama at Birmingham, Birmingham, AL, U.S.A.

[2]Department of Psychiatry, Harvard Medical School and Massachusetts General Hospital, Boston, MA, U.S.A.

[3]Brain Imaging and Modeling Section, NIDCD, NIH, Bethesda, MD, U.S.A.

Abstract

Exaggerated reactivity to food cues in obese women appears to be mediated in part by a hyperactive reward system that includes the nucleus accumbens, amygdala, and orbitofrontal cortex. The present study used fMRI to investigate whether differences between 12 obese and 12 normal-weight women in reward-related brain activation in response to food images can be explained by changes in the functional interactions between key reward network regions. A two-step path analysis/General Linear Model approach was used to test whether there were group differences in network connections between nucleus accumbens, amygdala, and orbitofrontal cortex in response to high- and low-calorie food images. There was abnormal connectivity in the obese group in response to both high- and low-calorie food cues compared to normal-weight controls. Compared to controls, the obese group had a relative deficiency in the amygdala's modulation of activation in both orbitofrontal cortex and nucleus accumbens, but excessive influence of orbitofrontal cortex's modulation of activation in nucleus accumbens. The deficient projections from the amygdala might relate to suboptimal modulation of the affective/emotional aspects of a food's reward value or an associated cue's motivational salience, whereas increased orbitofrontal cortex to nucleus accumbens connectivity might contribute to a heightened drive to eat in response to a food cue. Thus, it is possible that not only *greater* activation of the reward

Address correspondence to: Luke E. Stoeckel, 1 Bowdoin Square, Suite 701, 7th Floor, Boston, MA 02114-2919, Phone: 617-643-4493-1054, Fax: 617-724-3726, lstoeckel@partners.org.
Luke E. Stoeckel, M.A., Department of Psychiatry, Psychological Assessment Center, 1 Bowdoin Sq., Suite 701, 7th Floor, Boston, MA 02114-2919, lstoeckel@partners.org
Rosalyn E. Weller, Ph.D., Department of Psychology, University of Alabama at Birmingham, 415 Campbell Hall, 1530 3rd Ave. S., Birmingham, AL 35294, reweller@uab.edu
James E. Cox, Ph.D., Department of Psychology, University of Alabama at Birmingham, 415 Campbell Hall, 1530 3rd Ave. S., Birmingham, AL 35294, jecox@uab.edu
Edwin W. Cook III, Ph.D., Department of Psychology, University of Alabama at Birmingham, 415 Campbell Hall, 1530 3rd Ave. S., Birmingham, AL 35294, ecook@uab.edu
Jieun Kim, Ph.D., Brain Imaging and Modeling Section, Voice, Speech and Language Branch, National Institute on Deafness and other Communication Disorders, National Institutes of Health, Bldg. 10, Rm. 8S235, 10 Center Drive, MSC 1407, Bethesda, MD 20892-1407, kimjieun@nidcd.nih.gov
Barry Horwitz, Ph.D., Chief, Brain Imaging and Modeling Section, Voice, Speech and Language Branch, National Institute on Deafness and other Communication Disorders, National Institutes of Health, Bldg. 10, Rm. 8S235, 10 Center Drive, MSC 1407, Bethesda, MD 20892-1407, horwitzb@nidcd.nih.gov

Conflict of Interest
The authors declare that they have no competing financial interests.

system, but also differences in the *interaction* of regions in this network may contribute to the relatively increased motivational value of foods in obese individuals.

Keywords

connectivity; food cues; obesity; reward system

The etiology of obesity appears to be explained, in part, by exaggerated reactivity to cues associated with foods, especially to high-fat, energy dense foods (e.g., [12]). The mechanism for the heightened motivational salience of these stimuli in obese individuals may be a hyperactive reward system, which includes the nucleus accumbens/ventral striatum (NAc), amygdala (AMYG), and orbitofrontal cortex (OFC). A previous functional magnetic resonance imaging (fMRI) study found increased activation of these regions in response to high-calorie food images in obese compared to normal-weight individuals ([77]; Fig. 1). Other studies exposing obese individuals or those with higher BMI's to food stimuli also found abnormal patterns of activation in these regions ([22], [23], [28], [43], [68]), as well as others ([40], [68]). Stimuli associated with high-calorie foods may trigger excessive motivation for non-homeostatic eating of these types of foods ([10], [11], [53]). This excessive non-homeostatic desire to consume foods has been termed incentive salience or "wanting" and appears to be largely regulated via the mesocorticolimbic dopamine system, which includes NAc, AMYG, and OFC (e.g., [6]).

Most human fMRI studies use a mass univariate statistical analysis approach to discern the functional characteristics of different macroscopic brain regions. Investigators often integrate information about the functional specialization of a group of regions to explain how these regions might interact to perform a given function. However, the only valid empirically based conclusions that can be drawn from such analyses relate to the magnitude and extent of activation in a given set of brain regions, not how these regions functionally interact. Connectivity analyses allow investigators to study how networks of brain regions interact to perform cognitive and behavioral functions (e.g., [34]). It is important to note that inferences from traditional activation studies do not directly transfer to connectivity studies. That is, there may be measured differences in the *magnitude* of brain activation between groups, but no group differences in *connectivity*, and vice versa (e.g., [52]).

Path analysis, a type of structural equation modeling, is a multivariate, hypothesis-based approach applied to functional neuroimaging to investigate directional relationships between a given set of connected brain regions ([51]). This is one method for analysis of effective connectivity, in this case meaning changes in activation of one brain region resulting from changes in activation in another region. Path models are developed based on *a priori* hypotheses and assume a causal structure, where A → B means changes in region A are hypothesized to *cause* changes in region B (e.g., [69]). Brain regions in a network model are typically selected based on previous functional neuroimaging studies, and connections between these regions are usually defined based on the known neuroanatomical connections, mostly from animal literature, assuming homology in brain regions between species (e.g., [69]). The estimated parameter values calculated using path analysis represent the quantification of the directional pathways between regions in the model. These path coefficients can then be used to make comparisons between connections within subjects in response to changes in task conditions or between subjects and groups within the General Linear Model (GLM) framework (e.g., [44], [64]).

The NAc, AMYG, and OFC function together as part of the reward system. There are strong anatomical connections between these regions (see Fig. 2; AMYG → OFC: [7], [16], [30],

[38], [60], [65], [71], AMYG → NAc: [30], [38], [71], and OFC → NAc: [7], [16], [17], [30], [38], [56], [60], [65], [71]). Although it is clear that NAc, AMYG, and OFC are more strongly activated in obese compared to normal-weight controls when viewing food images, particularly high-calorie food images ([77]), it is uncertain whether activation in these regions relates to some common underlying reward process (e.g., incentive salience or motivation to approach and consume a reward) or whether there are different processes (e.g., hedonics or the pleasure component of reward and/or learning) that account for this activation pattern (see [8] for a discussion of these different reward processes). The NAc, AMYG, and OFC each have numerous functional properties. The NAc/ventral striatum functions as an interface between reward-related processing, homeostatic mechanisms, and motor output (e.g., [41]), but may also code for reward value ([57]). The OFC may encode multimodal sensory representations of food and food cues ([10], [11]). Together, AMYG and OFC may mediate the associative processes whereby food-related stimuli acquire incentive salience or other motivational properties (e.g., [6], [31]), but both also code for hedonic value, AMYG via bottom-up and OFC via top-down processes ([7]).

In this study, we used the fMRI data of Stoeckel et al. [77] and a two-stage path analysis plus GLM approach to investigate the interactions of key reward structures (NAc, AMYG, and OFC) in a simple network to determine whether these structures function together in response to images of high- and low-calorie foods differently in obese and normal-weight individuals. We expected to find effective connections between brain regions as specified in our model in normal-weight controls in response to high- and low-calorie food images. In addition, we expected to find a number of altered effective connections in our obese group that might help explain why foods have increased motivational potency for these individuals.

Materials and methods

The data used for the path analysis were the same data reported in Stoeckel et al. [77]. With the exception of the section discussing the methods of path analysis, the information below is provided in greater detail in Stoeckel et al. [77].

Participants

Participants were 12 obese (Body Mass Index, BMI = 30.8 – 41.2) and 12 normal-weight (BMI = 19.7 – 24.5) right-handed women recruited from the University of Alabama at Birmingham (UAB) community. There were no group differences on mean age (obese: 27.8, SD = 6.2; control: 28, SD = 4.4), ethnicity (obese: 7 African-American, 5 Caucasian; control: 6 African-American, 6 Caucasian), education (obese: 16.7 years, SD = 2.2; control: 17.2, SD = 2.8), or mean day of the menstrual cycle (obese: day 6.8, SD = 3.1, control: day 5.7, SD = 3.3, all in the follicular phase). Participants were recruited with advertisements placed in the UAB newspaper and fliers placed at various locations on the UAB campus. They were informed that the purpose of the study was to look at patterns of brain activity in "hungry" participants of different BMI's in response to visual images of various objects such as foods and control images. Individuals were excluded based on multiple health-related criteria, including a positive eating disorder history, active dieting or participating in a weight-loss program, or weight > 305 pounds (138 kg) with girth > 64 inches (163 cm), the latter due to scanner limitations. All participants signed a written informed consent after the study procedures and risks involved had been explained. All procedures were reviewed and approved by the Institutional Review Board for Human Use at UAB.

Stimuli

The stimuli used during the imaging session consisted of 252 color pictures, all of consistent size, resolution, and luminance ([77]). The 168 food images were subdivided into low-calorie and high-calorie categories, each consisting of 84 unique images. Low-calorie food images consisted of such low-fat items as steamed vegetables and broiled fish. High-calorie foods were primarily items high in fat such as cheesecake or pizza. Control stimuli consisted of images of cars, which varied widely in make, model, age, and color. The car images were intended as moderately interesting control stimuli that matched the low-calorie images on pleasantness based on results from Stoeckel et al. [77], with the high-calorie foods rated higher.

Procedure

After thorough screening to validate BMI and verify other study criteria, participants were scheduled for the fMRI session. They were instructed to eat a normal breakfast between 7–8 A.M. but to skip lunch and consume only water so that they had fasted for approximately 8–9 h before being imaged between 3–5 P.M. There were no group differences on subjective hunger ratings.

While participants were in the magnet, visual stimuli were presented in a block design format, with a total of six 3:09 min runs per imaging session. Each run consisted of two 21 s epochs each of cars (C), low-calorie foods (LC), and high-calorie foods (HC) pseudorandomly presented to the participants. Within each 21 s epoch of food or car images, seven individual images were each presented for 2.5 s. A 0.5 s gap separated the images, and a 9 s gap separated the epochs. All gaps consisted of a gray blank screen with a fixation cross. Each run consisted of 63 volumes for a total of 378 volumes across six runs, of which 84 volumes were acquired during each of the car, low-calorie food, and high-calorie food exposures. The visual images were presented by a laptop computer running VPM software ([18]). Images were projected onto a screen behind the participant's head and viewed via a 45° single-surface rear-projecting mirror attached to the head coil. Participants were financially compensated for their participation. All procedures were reviewed and approved by UAB's Institutional Review Board for Human Use.

MRI acquisition and processing

Functional MRI data were acquired using a Philips Intera 3T ultra-short bore magnet equipped with a sensitivity encoding (SENSE) head coil. Images were collected using a single-shot T2*-weighted gradient-echo EPI pulse sequence. We used TE = 30 msec, TR = 3 sec, and an 85° flip angle for 30 axial slices 4 mm thick with a 1 mm interslice gap, a scan resolution of 80 × 79, reconstructed to 128 × 128, and with a 230 × 149 × 230 mm FOV. The first four scans were discarded to allow the magnet to achieve steady-state magnetization.

Data were preprocessed (motion correction, normalization to the MNI coordinate system using the SPM2 EPI template, and smoothing with a 6 mm FWHM Gaussian filter) using the SPM2 software package (Wellcome Dept. Imaging Neuroscience, London, UK). No data sets failed to meet the movement inclusionary criteria, which were that movement before correction was < 2 mm in translational movement and < 2° in rotational movement (details in [77]).

Data analysis

fMRI data—Block-design blood oxygen level dependent (BOLD) responses were analyzed within the context of the General Linear Model on a voxel by voxel basis as implemented in

SPM2 ([27]). The time course of brain activation was modeled with a boxcar function convolved with the canonical hemodynamic response function (HRF) and a temporal derivative function. The data were high-pass filtered (1/128 Hz) to remove low frequency drifts. A first order autoregressive model was also implemented to correct for autocorrelations in the error term of the fMRI model.

A two-stage random-effects procedure was used for the statistical analysis to account for both within-subject and between-subject variability. First, the fMRI data from each individual participant were used to generate statistical contrasts of the parameter estimates in order to test the differences between the time points corresponding to the high-calorie and low-calorie foods. Results of a previous study ([77]) found group differences in patterns of reward-related activation, with the obese group exhibiting greater activation to high-calorie foods and controls to low-calorie foods. The food > control stimuli contrast was then entered into second-level one-sample t-test analyses for the within-group comparisons to localize the group maxima for our regions of interest (ROI): bilateral NAc, AMYG, and middle OFC ($p < .05$, uncorrected).

The ROI's for AMYG and OFC were defined using the WFU Pickatlas and the AAL and Talairach Daemon atlases ([47], [49], [79]). Because NAc was unavailable in these libraries, we drew a sphere 6 mm in radius with the WFU Pickatlas centered at a voxel location determined by averaging voxel location dimensions from relevant fMRI studies ([1], [54], [58]). The classification of the regional location of activated voxels was verified by using the WFU Pickatlas and visual inspection of the data using a human brain atlas ([48]).

Path analysis

Path analysis was used to determine the strength and direction of the relationships (effective connections) between observed variables (ROIs), estimated using simultaneous regression equations via maximum likelihood estimation. This is one of the most common modeling approaches used to study effective connectivity ([69]). We used a two-step path analysis/GLM approach, following a similar method as Kim et al. [44]. For each participant: (1) ROIs were selected to include in the model, (2) the time series data were partitioned into two groups associated with volumes for the two task conditions (high- and low-calorie foods), (3) summary data were extracted for each condition for each ROI, (4) a model was designated that specified the interactions of the ROIs, (5) the variance-covariance (number of scan volumes X number of ROIs) matrix for each condition was calculated, and (6) the path coefficients for the connections between ROIs in the models were estimated via maximum likelihood estimation. Repeated-measures ANOVA was then used to determine within-group (i.e., condition) and between-group differences in the model connections using the path coefficients from the models for each individual.

Model specification—The regions included in the model (OFC, AMYG, and NAc) are components of what has been termed the “motive circuit” ([63]), involving the mesocorticolimbic dopamine system ([6], [36], [39], [45], [63], [66], [73], [80], [83]). The connections in the model were defined partly based on the known anatomical connectivity of the structures in this network, but also considering methodological constraints (e.g., the temporal resolution of fMRI and the problem of identification with non-recursive models using structural equation modeling; [7], [30], [38], [60], [65], [71]; Fig. 2). In order to estimate reliable path coefficient values, the model was constrained to be recursive (i.e., no reciprocal paths were included in the model).

The same path model was constructed for each subject. To allow for inter-subject variability, we defined the exact coordinates of each region for each hemisphere from the local maximum of each participant’s statistical map within 12 mm of the group maximum (within

the same anatomical region) resulting from the foods > cars contrast ($p < .05$, uncorrected; [52]). The MNI coordinates of the regions were NAc, left (x, y, z): −6, 10, −10 [controls] and −10, 14, −6 [obese]; NAc right, (x, y, z): 6, 10, −10 [controls] and 6, 12, −10 [obese]; AMYG, left (x, y, z): −26, −2, −20 [controls] and −20, 0, −24 [obese]; AMYG, right (x, y, z): 22, 0, −20 [controls] and 24, 2, −24 [obese]; OFC, left (x, y, z): −22, 36, −10 [controls] and −22, 30, −14 [obese]; OFC, right (x, y, z): 26, 36, −14 [controls] and 26, 30, −4 [obese]. For each region, the principal eigenvariate of the time series was extracted from a 4-mm sphere centered at the subject-specific local maximum. The principal (i.e., 1st) eigenvariate is a summary measure, similar to a weighted mean robust to outliers, based on the variance of all the voxels included within the sphere 4 mm in radius.

The regional time series data (principal eigenvariate values) were then separated into two data sets: time points associated with (1) the high-calorie foods and (2) the low-calorie foods. To account for the hemodynamic lag, we assumed a 6 s (2 TR) physiological delay between the onset and offset of our two conditions and adjusted the data we extracted accordingly ([32]). This resulted in two 84 (number of scan volumes) X 6 (number of ROIs) matrices of data for each condition (high- and low-calorie foods) for each participant.

Path parameter estimates—A path model was fit to the data matrix for both the high-calorie and low-calorie foods independently for each participant. The free path coefficients were estimated by minimizing the discrepancy between a correlation matrix observed from the fMRI data and a correlation matrix predicted by the model using LISREL software (Version 8, SSI Scientific Software). The standardized parameter estimates (similar to β's in regression), or path coefficients, for each connection (AMYG → OFC, OFC → NAc, and AMYG → NAc) within each hemisphere (left and right) from both models (high- and low-calorie foods) for each participant were imported into SPSS for subsequent analyses. A mixed-model ANOVA was conducted for each of the three connections, in which the factors were group (obese versus control), food category (high- versus low-calorie) and hemisphere. As this was an exploratory study, we tested for the significance of specific path coefficients as long as the omnibus models showed at least near-significant effects ($p < 0.10$). For each group, one sample t-tests were used to test whether the path coefficients in the high- and low-calorie food models were significantly different from zero, indicating connectivity as specified. Pairwise comparisons were used to test the differences in path coefficients for each hemisphere (left and right) for within-group (high-calorie vs. low-calorie foods) and between-group comparisons (obese vs. controls for high-calorie and low-calorie foods, independently). Paired t-tests were used for within-group comparisons and independent samples t-tests were used for between-group comparisons.

Results

All of the estimated path coefficients were significantly different from zero for the obese group and controls for both hemispheres in both the high- and low-calorie food models, consistent with the specified connectivity model (p values < 0.001; Table 1).

Between-group comparisons

OFC → NAc—There was no main effect of group for the OFC → NAc connection, although there was a trend ($F [1,22] = 3.70$, $p = 0.067$), indicating greater connectivity for the obese group (0.53 ± 0.06) compared to the controls (0.41 ± 0.06). There were no significant group X category or group X category X laterality interactions, although there was a trend towards a group X laterality interaction ($p = 0.059$). Left-side path coefficients from OFC → NAc were significantly higher in the obese group for both high- and low-calorie foods (p values < .03; Fig. 3).

AMYG → OFC—There was a main effect of group such that the mean connectivity from AMYG → OFC was less for obese participants (0.64 ± 0.07) compared to controls (0.84 ± 0.07), indicating a relatively stronger directional relationship in brain activation between these structures in response to foods in controls ($F [1,22] = 4.46$, $p = 0.046$). There were no significant group by category or group by laterality interactions, although there was a trend ($p = 0.066$) toward a group by category X laterality interaction. Subsequent analyses showed that path coefficients were significantly greater in controls for high-calorie foods bilaterally and from right AMYG → right OFC for low-calorie foods (p values < .05; Fig. 3).

AMYG → NAc—There was a main effect of group for the mean AMYG → NAc connection such that there was weaker connectivity for the obese group (0.35 ± 0.05) compared to control participants (0.49 ± 0.05; $F[1,22] = 6.00$, $p = 0.023$). There were no significant group X category or group X category X laterality interactions, although there was a trend towards a group X laterality interaction ($p = 0.09$). Pairwise comparisons indicated that left-side path coefficients were significantly greater for controls for both high- and low-calorie foods (p values < .05; Fig. 3).

Within-group comparisons of high- vs. low-calorie food conditions

The path coefficients from AMYG → OFC bilaterally were significantly greater for the high-calorie foods category comparison in the controls (left: $p = 0.007$, right: $p = 0.002$; see Fig. 4). None of the path coefficients differed significantly between the high- and low-calorie food conditions within the obese group.

Discussion

Previous research has shown that food cues, especially those associated with high-calorie foods, trigger hyperactivity in brain regions including NAc, AMYG, and OFC thought to mediate or at least code for motivational and emotional processes in obese individuals (e.g., [68], [77]). In the present study, we tested whether there were differences in network connections between NAc, AMYG, and OFC in response to high- and low-calorie food images within and between obese and normal-weight groups. It is important to note that this is the first human connectivity study using functional neuroimaging to measure the interaction of brain regions in a reward network. We found aberrant connectivity in the obese group in response to both high- and low-calorie food cues compared to normal-weight controls. Specifically, it appears that the obese group has a relative deficiency in AMYG-modulated activation of both OFC and NAc, but a tendency toward excessive influence of OFC's modulation of activation of NAc. Thus, it is possible that not only *greater* activation of the reward system, but also differences in the *interaction* of regions in this network may contribute to the relatively increased motivational value of foods in obese individuals.

The reward model

All path connections among NAc, AMYG, and OFC were significant for both high- and low-calorie food models in both the obese group and normal-weight controls, consistent with known anatomical connections among these regions ([7], [16], [17], [30], [38], [56], [60], [65], [71]). This network is innervated by the ventral tegmental area, which releases dopamine to this circuit in response to motivationally salient events ([9], [39], [71]). However, the projections between NAc, AMYG, and OFC as illustrated in Fig. 2 are glutamatergic ([39], [71]).

This NAc, AMYG, and OFC reward network is a subcircuit of a larger "motive circuit" thought to activate and direct behavior in response to motivationally-relevant stimuli ([39], [63]). The NAc, AMYG, and OFC, in particular, have important reward-related functions

that likely contribute to both general and food-specific motivational processes ([6], [10], [11], [36], [39], [45], [63], [66], [73], [80], [83]). The NAc/ventral striatum has been conceptualized as the 'limbic-motor' interface ([55]) and appears to be involved in processing related to Pavlovian conditioning, incentive salience, and reward availability, value, and context ([13], [15], [21]). This region, in conjunction with ventral pallidum via opioid-mediated mechanisms, may also code for hedonic value ([9], [10], [11], [74], [75]). The NAc/ventral striatum also appears to code for the general motivational milieu (e.g., [14]), which would allow for the hierarchical organization of incoming reward-related signals. For food reward, the NAc/ventral striatum appears to show preferential involvement in the encoding of cues associated with foods (versus food consumption) and may integrate homeostatic and non-homeostatic signals to modulate motivational state ([42], [76]). This region might also code for the relative reward value of available food stimuli ([57]). The AMYG appears to be involved in motivationally-relevant associative processes ([61], [62]). In addition to coding for more general affective and motivational properties, AMYG activity may relate to the specific properties of food-related stimuli ([2]). The OFC appears to be a key region for translating reward value into hedonic experience ([46]), processing the temporal and certainty characteristics of reward ([14]), and is involved in motivation-related learning processes in conjunction with AMYG ([24], [59]). The OFC shows multimodal responses to food cues ([67]) and has been referred to as the 'tertiary taste area', following gustatory processing in insular cortex ([10], [11]).

Significance of group differences in connectivity

OFC → NAc—Obese women showed greater left hemisphere OFC → NAc connectivity than controls did for both high- and low-calorie foods. This path may have been strengthened in the obese group by the combination of increased OFC activation by food pictures and elevated dopamine (DA) function within the NAc in these individuals. Horvitz [33] has proposed that DA acts to gate glutamatergic reward inputs from OFC to NAc. Because of this gating, in the presence of high DA function within NAc, high levels of activity within OFC become more effective in further increasing NAc activity. Although the role of DA in obesity is controversial ([20], [29], [81]), indirect evidence suggests elevated DA function within the reward system of mild to moderately obese individuals (e.g., [20]), such as those in our sample. We speculate that the OFC → NAc path may be a key to the proposed positive relationships among food cue reactivity, greater intake, and high BMI ([25], [78]) because of strong coupling of exaggerated subjective reward value of food cues mediated by the OFC with output pathways accessed by the NAc. Finally, because of suggested parallels between obesity and drug addiction (e.g., [82]), it is noteworthy that addiction investigators have proposed that dysregulated PFC (including OFC) → NAc synaptic glutamate transmission explains increased motivation for drugs in response to drug-related cues ([37], [39]).

AMYG → OFC and AMYG → NAc—In the obese participants compared to controls, we found reduced path coefficients from AMYG to both OFC and NAc. These differences were significant for AMYG → OFC bilaterally for high-calorie foods and in the right hemisphere for low-calorie foods. AMYG → NAc connectivity was lower in the obese group in the left hemisphere for both high-calorie and low-calorie foods. Although the relevance of these group differences for obesity is not clear, it is possible that reduced connectivity from the AMYG to these structures may impair flexibility in updating of reward value. Basic learning whereby stimuli associated with primary rewards acquire motivational value may occur in the AMYG ([5]). The AMYG → OFC projection may transfer basic motivationally relevant associative information to the OFC, which uses information from the AMYG to determine subjective value and influence subsequent instrumental choice behavior ([15]). As an example of the importance of this pathway for modifying reward value, Baxter and

colleagues [3] found that rhesus macaques failed to change their behavior during a reward devaluation task after the connection between AMYG and OFC was disrupted. In a cue-outcome learning paradigm, Schoenbaum and colleagues [70] found that disrupting the AMYG → OFC pathway via lesioning resulted in more cue-selective OFC neuron firing in response to the sensory as opposed to associative properties of the cue. With regard to ingestive behavior, a deficient AMYG → OFC connection in the obese participants may indicate suboptimal transfer of basic affective/emotional value regarding foods and food cues important for updating the subjective reward value of these cues to facilitate flexibility in food intake behavior. Compared to normal-weight individuals, the reward value of foods and food cues may be more strongly driven by the sensory properties of the foods and food cues for obese individuals. In addition, the sensory-driven reward value of the foods and food cues may be less malleable in the face of changing reward contingencies.

Similar to the AMYG → OFC connection, a deficient connection in the obese from AMYG → NAc might indicate the basic hedonic signal that serves to modulate the reward value of foods or food cues (AMYG) is not appropriately weighted with other signals (e.g., motivational, homeostatic) before the appropriate ingestive behavior is determined ([84]).

Limitations and caveats

1. Specifying a model using path analysis in fMRI can be a challenge because the number and combination of connections between regions increases substantially with every additional region included in the model, which makes estimating these path coefficients reliably and interpreting the findings more difficult. For instance, in this study with 3 regions per hemisphere (6 regions total), there are $k = N(N + 1) / 2 = 21$ degrees of freedom per data set ($k = 42$ degrees of freedom for the two models tested) allotted to estimate the effects of interest. Twelve degrees of freedom are used to estimate the variances associated with each region in both models (6 regions per model × 2 models). With a *minimum* of 5 data points necessary to estimate the parameter values for each path in the model reliably ([4]), this leaves a maximum of 30 estimable paths for two models with 6 regions each (15 estimable paths per model). This limits the complexity of the model that can be tested using path analysis and is one reason we chose not to include interhemispheric connections in our models.
2. We chose the two-stage SEM/GLM approach in order to directly test for group differences between connections in a hypothesized model and were not as interested in comparing the fit of the model between groups per se. This approach is different from the traditional fMRI and path analysis methodology termed the “stacked model approach” comparing model fit between tasks or groups ([50]). However, Protzner and McIntosh [64] recently reported that absolute model fit information is not necessary in order to generate reliable parameter estimates using path analysis.
3. Another limitation of this study relates to the power to detect differences between the path coefficients estimated in our models due to the small sample sizes used for each group. With larger group sizes, our trend level findings would likely have reached statistical significance.
4. We did not include the ventral tegmental area (VTA), the source of dopamine within the mesocorticolimbic circuit proposed to mediate many of the processes associated with reward ([26], [35], [72]), in our model due to methodological limitations related to BOLD fMRI that make detecting activation in brainstem regions like the VTA difficult ([19]).

Conclusions and Summary

In summary, our neuroimaging study found aberrant reward network connectivity in obese individuals compared to controls, with reduced connectivity from AMYG to OFC and NAc and increased connectivity in OFC → NAc in these participants. These results add to previous reports in showing that there is not only exaggerated reward system activation in response to foods, but also an abnormal interaction between regions in this network in obese individuals. In particular, we think overeating in obese individuals might be influenced by two mechanisms: (1) increased OFC → NAc connectivity might contribute to heightened drive to consume foods and (2) deficient connectivity from AMYG might result in suboptimal modulation of the affective/emotional aspects of a food or food cues reward value. Without the appropriate affective/emotional information to signal the devaluation of foods or food cues following food intake, heightened drive may overwhelm homeostatic mechanisms leading to hyperphagia and increased weight gain. Admittedly, we tested a simple reward network. Further studies are necessary to investigate connectivity in the reward system and how these regions might interact with homeostatic mechanisms in the hypothalamus and brainstem, as well as the cognitive mechanisms of food intake control in the prefrontal cortex. It will also be interesting to determine how individual differences and interoceptive and exteroceptive factors modulate this reward network in order to better understand how reward mechanisms influence ingestive behavior.

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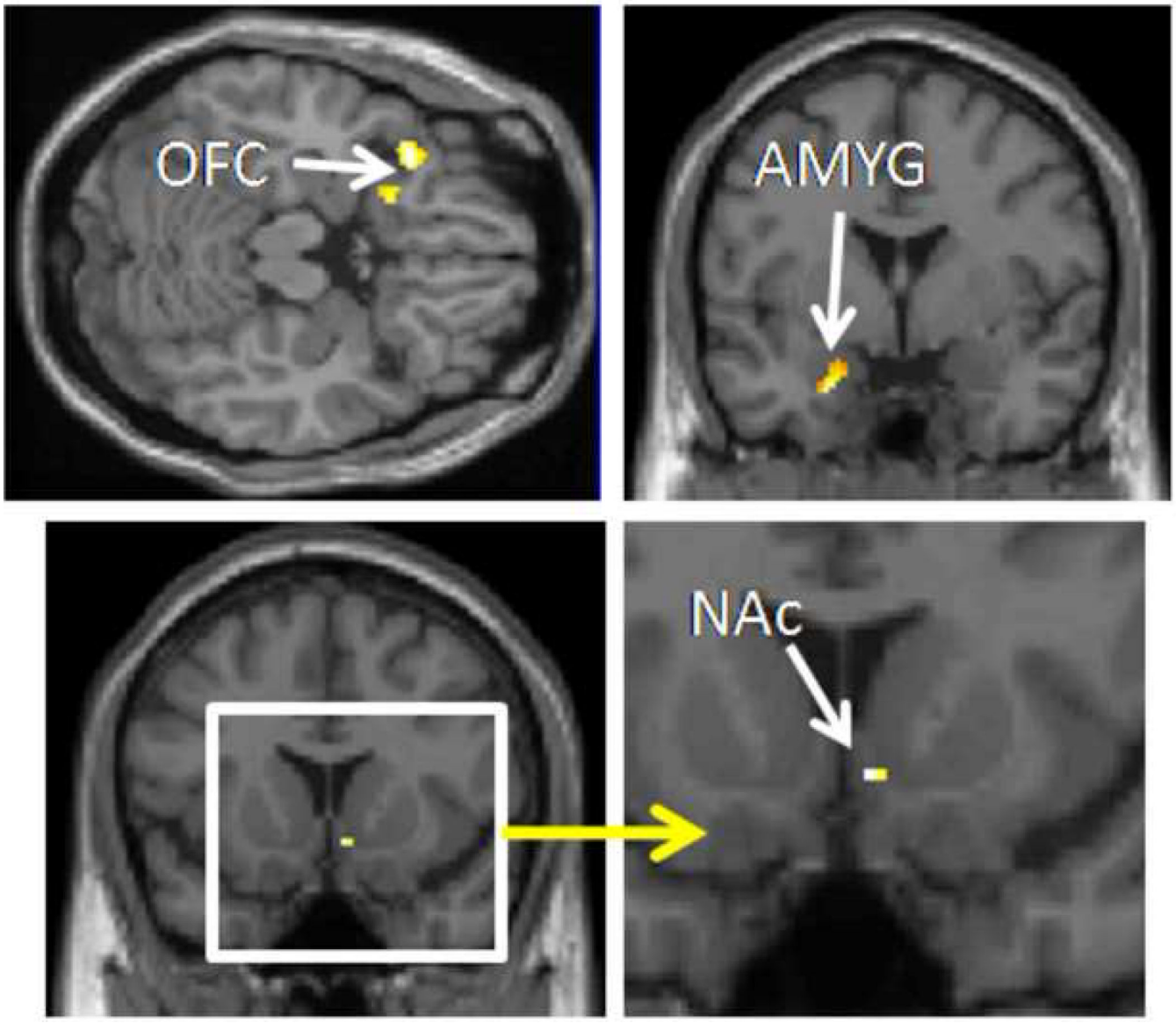

Fig. 1.

Greater activation found in obese compared to control participants to high-calorie foods > cars in (A) left Lat OFC (axial view). Greater activation found in obese compared to control participants to high-calorie > low-calorie foods in (B) left AMYG (coronal view) and (C) right NAc (coronal view), enhanced view of image on right. Activation is overlaid on the SPM2 single-subject T1 template.

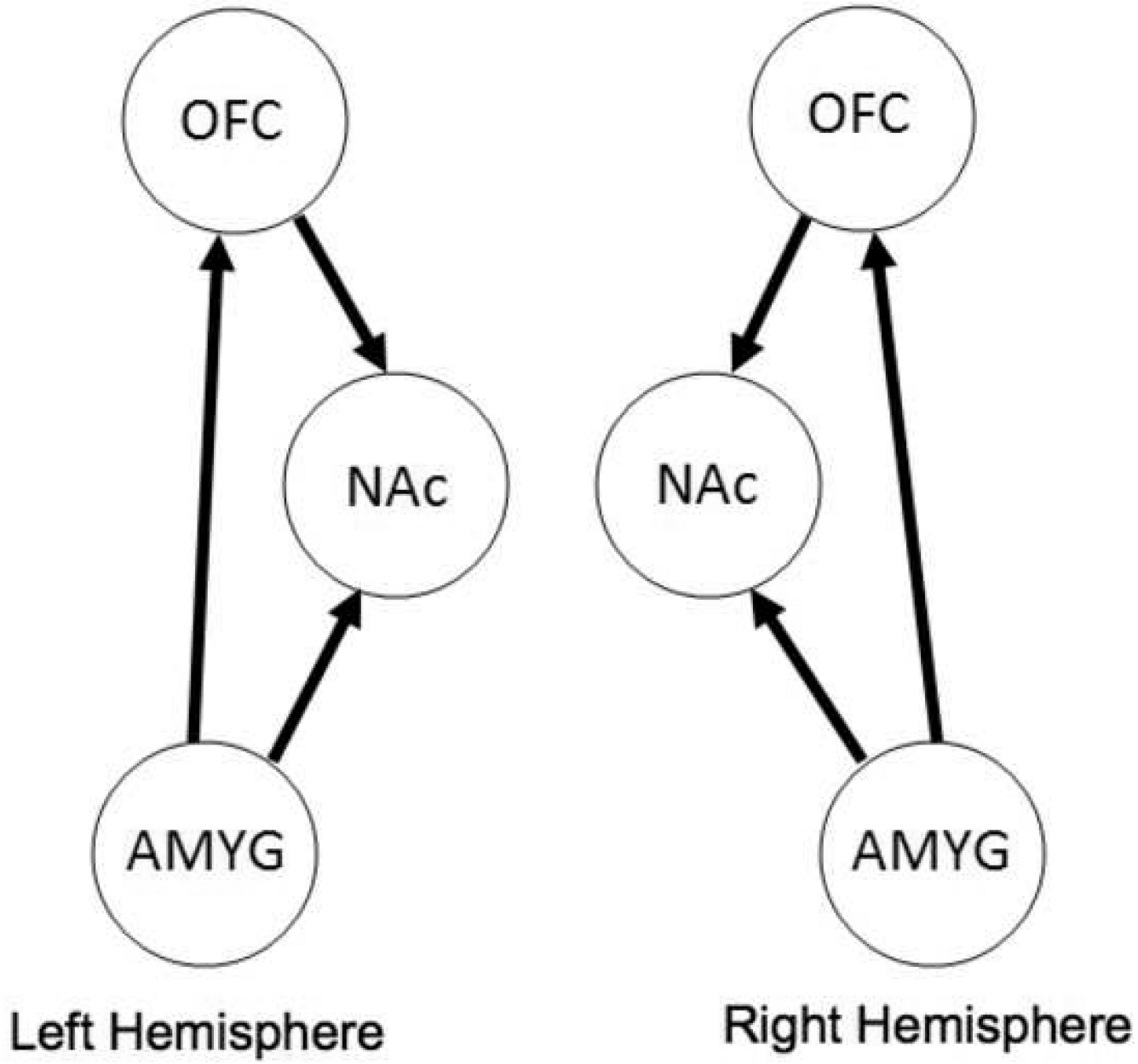

Fig. 2.
The path model for the reward network tested including the three regions (NAc, AMYG, and OFC) for both the left and right hemispheres (circles) and their directional connections (indicated by the arrows).

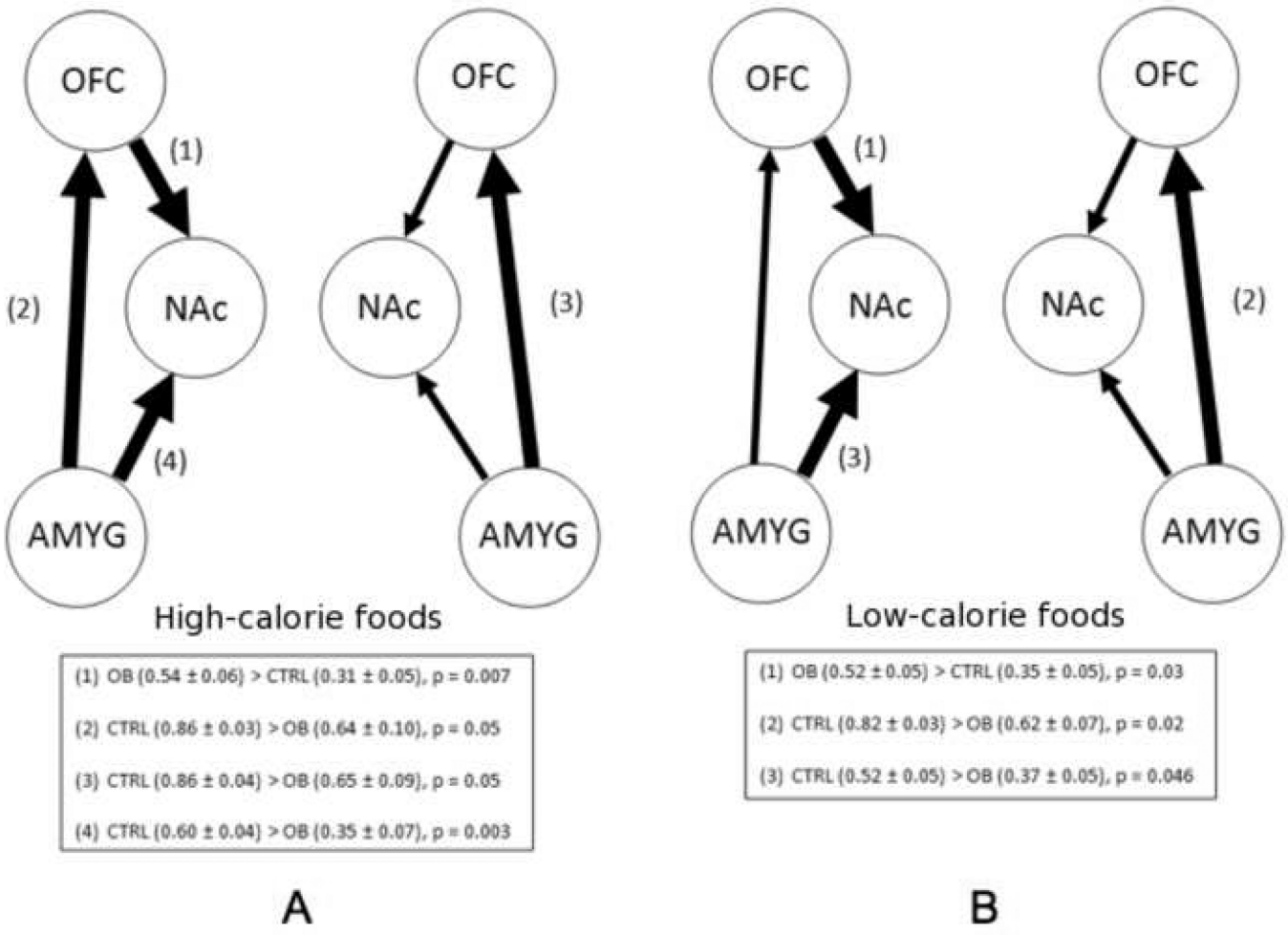

Fig. 3.

Group comparisons (obese vs. controls) related to the path coefficients for the (A) high-calorie foods and (B) low-calorie foods. Thicker arrows indicate significant or trend-level differences. OB = obese, CTRL = controls. All other conventions as mentioned previously.

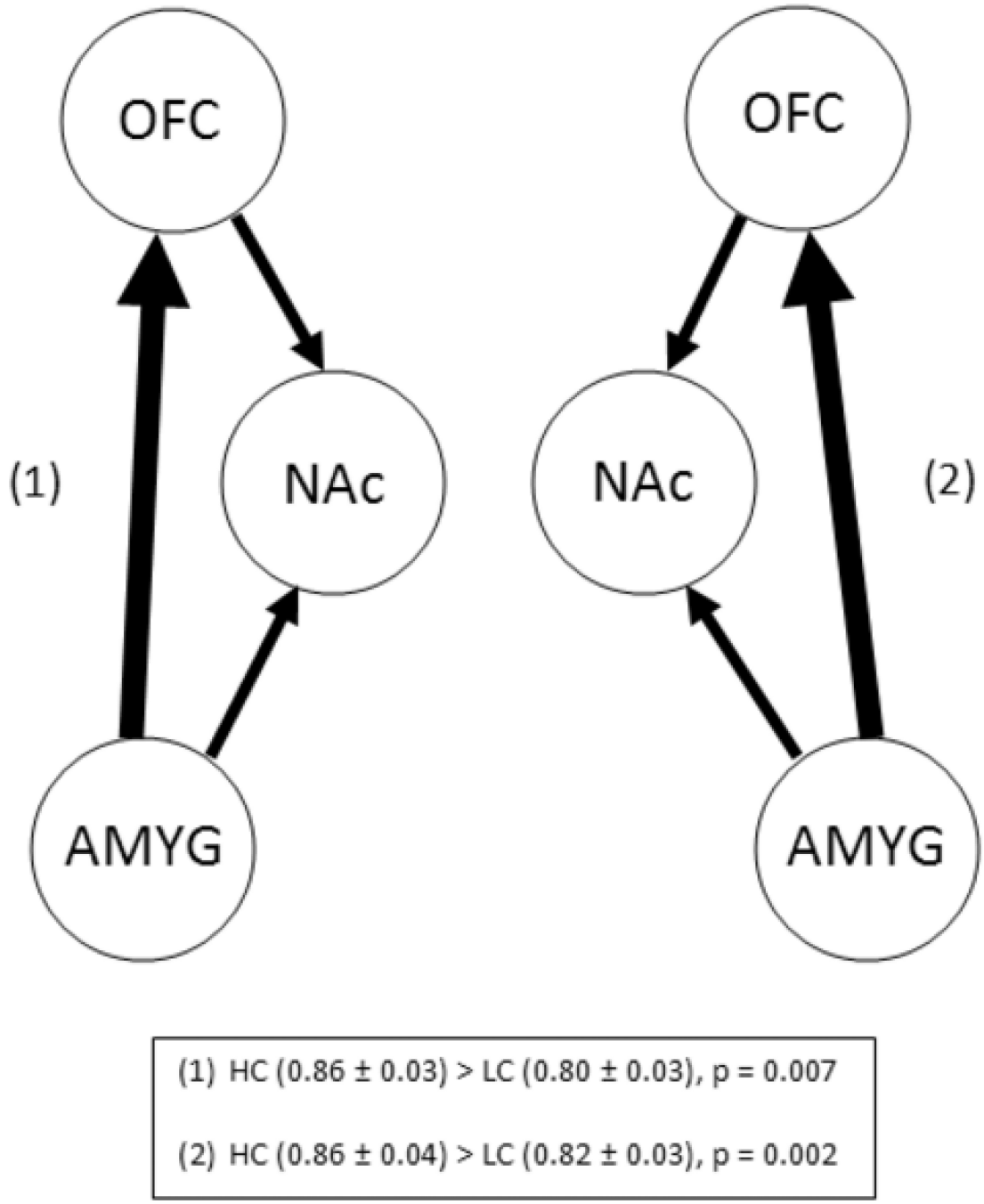

Fig. 4.

Food category (high-calorie foods vs. low-calorie foods) comparisons within the control group. Thicker arrows indicate significant or trend-level differences. HC = high-calorie foods, LC = low-calorie foods. All other conventions as mentioned previously.

Table 1

The path coefficients for the connections tested in the reward model for the high-calorie food and low-calorie food conditions for the obese and normal-weight groups.

Path Connections	HC (Obese)	HC (Controls)	LC (Obese)	LC (Controls)
L AMYG → L OFC	0.64 ± 0.10	0.86 ± 0.03	0.65 ± 0.09	0.80 ± 0.03
R AMYG → R OFC	0.65 ± 0.09	0.86 ± 0.04	0.62 ± 0.07	0.82 ± 0.03
L AMYG → L NAc	0.35 ± 0.07	0.60 ± 0.04	0.37 ± 0.05	0.52 ± 0.05
R AMYG → R NAc	0.36 ± 0.06	0.45 ± 0.06	0.32 ± 0.04	0.39 ± 0.06
L OFC → L NAc	0.54 ± 0.06	0.31 ± 0.05	0.52 ± 0.05	0.35 ± 0.05
R OFC → R NAc	0.52 ± 0.08	0.49 ± 0.06	0.57 ± 0.05	0.52 ± 0.06

L = left, R = right, HC = high-calorie foods, LC = low-calorie foods. All other conventions as in the paper.