

Association of Leptin With Food Cue–Induced Activation in Human Reward Pathways

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Context: Overlapping neurobiological pathways between obesity and addiction disorders are currently in discussion. Whereas the hypothalamic regulation of energy homeostasis by endocrine feedback signals has been widely investigated, its interplay with mesolimbic reward-associated pathways represents a rich field of future research.

Objective: To assess changes in regional brain activation in response to food-related cues in association with body mass index (BMI; calculated as weight in kilograms divided by height in meters squared) and the plasma concentration of the appetite-regulating peptide leptin.

Design: Case-control study.

Setting: Academic addiction and brain imaging center, Central Institute of Mental Health, Mannheim, Germany.

Participants: Twenty-one obese subjects (BMI >30) and 23 age- and sex-matched nonobese control subjects (BMI 18.5–24.0) recruited by advertisements.

Main Outcome Measures: Regional brain activation (blood oxygen level–dependent response) in response to visual cue presentation and association of the brain activation with BMI and plasma leptin concentration.

Results: Significant positive relationships were observed for food cue–induced brain activations in the ventral striatum in association with the plasma concentration of leptin ($r=0.27$; $P=.04$) and with BMI ($r=0.47$; $P=.001$).

Conclusions: Data suggest a physiological role of satiety factors in modulating the responsivity of mesolimbic circuits to food cues. Moreover, an altered homeostatic feedback regulation of reward pathways might explain addictionlike behavior and the inability of obese patients to adapt food intake to physiological needs.

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OBESITY IS A VERY EXPENSIVE health problem that is growing more prevalent every year.^{1–3} One of the major difficulties with treating obesity is that, even after successful diets, most patients relapse into their previous unhealthy eating habits, thereby regaining most, if not all, of their initial weight.⁴ The specific neural pathways and mechanisms underlying this excessive calorie consumption are not completely understood.⁵ While the influences of genetic predisposition^{6,7} and environmental factors⁸ of obesity are well known, a clearer understanding of neuronal mechanisms that interact with metabolic regulation is needed to better facilitate the prevention and treatment of obesity.

According to several studies, food intake is associated with dopamine release in striatal regions.^{9–11} Some researchers have ad-

vanced the view that severe obesity operates similarly to drug addiction, running along the same neuronal circuits.^{12–14} Neuroimaging-based approaches using positron emission tomography have found evidence of reduced striatal D₂ receptor availability in obese and drug-addicted subjects compared with healthy control subjects.¹⁵ Wang et al¹⁵ also found D₂ receptor availability in obese subjects to be negatively correlated with body mass index (BMI). Two studies applying functional magnetic resonance imaging (fMRI) allowed a closer understanding of the role of cue reactivity in obesity and food addiction: the first associated the visual presentation of high-calorie food cues with increased neural activation in mesolimbic areas,¹⁶ and the more recent second study associated the increased activation in the dorsolateral prefrontal cortex and caudate in anticipation of the receipt of food with

the Yale Food Addiction Scale score, operationalizing substance-dependence symptoms in eating behavior.¹⁷

In recent years, evidence has accumulated that the appetite-regulating peptide leptin is involved in food-related reward mechanisms. It has been suggested that leptin, which is secreted by white adipocytes, acts as a messenger signaling satiety at the hypothalamic level, thus diminishing food intake.¹⁸ However, leptin was additionally shown to bind to specific receptors on dopaminergic neurons in the ventral tegmental area (VTA), inhibiting dopamine signaling in the nucleus accumbens.^{19,20} Because it affects the hypothalamic and the mesolimbic pathways, leptin might provide a link between energy homeostasis and reward-related behavior.^{21,22} Moreover, there is evidence that an elevated leptin concentration is associated with addictive behavior,²³⁻²⁷ strengthening the hypothesis that leptin interacts with mesolimbic reward pathways.

The first evidence of the possible influence of leptin on fMRI cue reactivity to visual food stimuli was found by 2 landmark studies on patients with leptin deficiency syndrome (LDS), a rare condition that causes hyperphagia and severe obesity.^{28,29} The study by Farooqi and colleagues²⁹ presented fMRI data from 2 adolescents 7 days before and after first-ever treatment with peripherally administered leptin. The 2 participants underwent scanning while they were presented with food images after having fasted and also after having eaten. Their hunger and satiety levels and the degree to which the food images appealed to them were assessed with the use of visual analog scales. When the participants were in a leptin-deficient state, the food images caused marked activation in the anteromedial ventral striatum and the posterolateral ventral striatum and correlated positively with their ratings of the food's appeal in both the fasted and fed states. After leptin treatment, their hunger decreased and their satiety increased after meals. Activation in striatal regions was also reduced, correlating only with the food-appeal ratings after having fasted. Those findings provided the first evidence that leptin acts on neural reward circuits governing visual food cues.²⁹ However, the studies left unanswered whether these or similar mechanisms are responsible for diet-induced obesity (DIO) in the general population.

Herein, we present the first study, to our knowledge, to investigate whether leptin levels are associated with the intensity of mesolimbic reactivity to food cues in obese and nonobese subjects. Our results might help elucidate the interaction between the homeostatic regulations of the energy balance and mesolimbic reward pathways, thereby enabling future research in obesity to define more effective treatment targets.

METHODS

PARTICIPANTS

Eighty-five obese individuals responded to our newspaper advertisements and were subjected to telephone prescreening. Only individuals meeting the following inclusion criteria were invited for a personal screening: age between 18 and 65 years; a BMI (calculated as weight in kilograms divided by height in meters squared) greater than 30; a waist circumference less than

150 cm (to be able to fit into our scanner); the capacity to give informed consent; no history or current diagnosis of any psychiatric, neurological, neoplastic, or untreated endocrine illnesses (with the exception of nicotine addiction); and no current intake of any psychoactive or antiobesity medications. Individuals with a history of surgical interventions in the gastrointestinal system (eg, gastric banding) or contraindications to fMRI scanning were also excluded. Of the individuals screened, 21 obese right-handed subjects (15 women and 6 men) with a mean BMI of 36.9 (range, 30.0-47.5) met the required inclusion criteria and were subsequently admitted into the study. For the control group, we used 23 healthy, age- and sex-matched, nonobese (BMI 18.5-24.0), right-handed subjects (15 women and 8 men) with a mean BMI of 22.1. Five obese participants and 7 controls were active smokers. All participants provided written informed consent, and the study was approved by the local ethics committee.

TESTING PROCEDURES

Testing for all participants began between noon and 3 PM. All participants ate a standardized breakfast of 500 kcal 6 hours before fMRI scanning.

Depressive symptoms were assessed with the Beck Depression Inventory³⁰ and nicotine use with the Fagerström Test for Nicotine Dependence.³¹ Eating habits were documented via self-report with the Three-Factor Eating Questionnaire.³² After completing the questionnaires (data not shown), physical measurements were taken. Before scanning, 30 mL of full blood was drawn from a cubital vein for use in neuroendocrine analyses.

LABORATORY ANALYSIS

Blood samples were anticoagulated with sodium EDTA (1 mg/mL of whole blood) and immediately cooled on ice. Plasma was stored at -80°C until analysis (maximum length of storage, 6 months). Hormonal analyses were performed at the Neurobiological Laboratory of the Department of Psychiatry, University of Hamburg (K.W.). To measure the leptin concentration, we used a human leptin radioimmunoassay kit (Millipore). The kit had a detection limit of 0.5 ng/mL for plasma concentrations of leptin; intra-assay and interassay coefficients of variation were below 8.5% for concentrations of 4.9 and 15.7 ng/mL, respectively.

fMRI TASK

We presented 18 blocks of food stimuli and 12 blocks of neutral stimuli to the participants while they underwent fMRI scanning. Each block consisted of 5 stimuli of the same category shown for 4 seconds each, resulting in a total block length of 20 seconds. The order of the stimulus blocks was pseudorandomized, and the pictures within each block were randomized for each subject. The food stimuli were arranged in 3 categories: salty high-calorie, sweet high-calorie, and low-calorie (both salty and sweet). Examples of the stimuli for the salty high-calorie and neutral categories can be found in **Figure 1**. The participants' food cravings were assessed with a visual analog scale that appeared after each block. The scale ranged from "very weak" to "very strong" and featured values ranging from 0 to 100. Participants had to rate their craving within 10 seconds. After completing the rating, a fixation cross was presented for a minimum of 10 seconds. The fMRI task lasted a total of 18 minutes.

Food stimuli were chosen from a set of pictures that were rated for their ability to induce food cravings by 44 voluntary participants at our institution (M.G., C.V., and S.L., unpublished data, August 2009). Neutral cues were taken from the International Affective Picture Series,³³ avoiding pictures of food-related items.

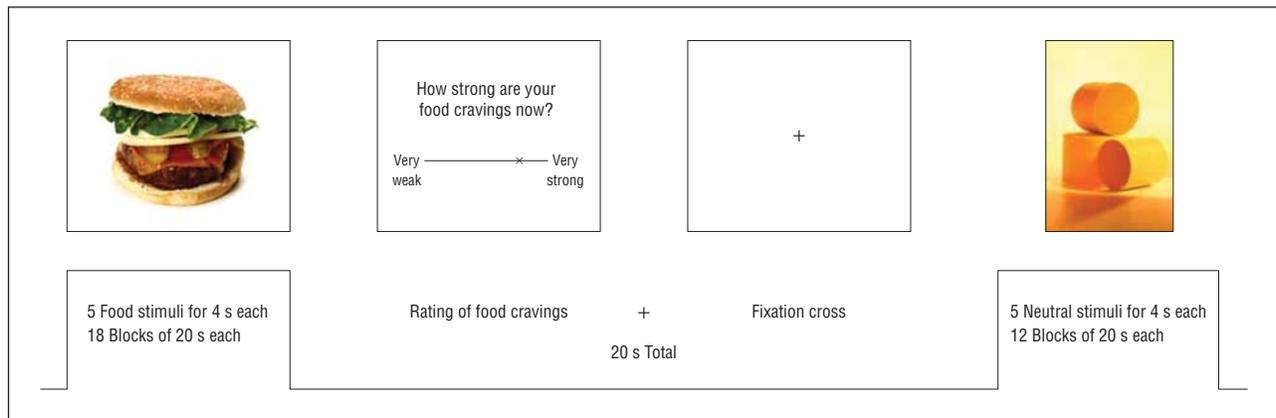


Figure 1. Functional magnetic resonance imaging block-design paradigm, including examples of food and neutral stimuli. We presented participants with 18 blocks of food stimuli and 12 blocks of neutral stimuli. In each block, 5 stimuli of the same category were shown for 4 seconds each. The order of the stimuli was pseudorandomized, whereas the pictures in each block were randomized for each subject. The subjects' food cravings were assessed with a visual analog scale after each block. The scale featured values ranging from 0 to 100 (very weak to very strong). Participants had to rate their food cravings within 10 seconds. After rating the craving intensity, participants were presented with a fixation cross for at least 10 seconds.

fMRI ACQUISITION

The scans were performed using a 3-T whole-body tomography scanner (MAGNETOM Trio with TIM technology; Siemens). We acquired T2*-weighted, echo planar images of the entire brain. These images were in a transversal orientation, 30° clockwise to the anterior commissure–posterior commissure line (repetition time, 2.41 seconds; echo time, 25 milliseconds; flip angle, 80°; 42 sections; section thickness, 2 mm; 1-mm gap; voxel dimensions, 3 × 3 × 3 mm³; field of view, 192 × 192 mm²; in-plane resolution, 64 × 64). We chose the short echo time and the 30° flip angle to anterior commissure–posterior commissure orientation to minimize susceptibility artifacts. We obtained a total of 453 images per subject. We also acquired a T1-weighted, 3-dimensional magnetization prepared rapid acquisition gradient echo data set consisting of 192 sagittal sections (section thickness, 1 mm; voxel size, 1 × 1 × 1 mm; field of view, 256 × 256 mm²; repetition time, 2300 milliseconds; echo time, 3.03 milliseconds; inversion time, 900 milliseconds; flip angle, 9°).

Images were presented to the subjects via goggles using an audio/video system (MRI Audio/Video Systems; Resonance Technology, Inc). We recorded the behavioral responses and presented the tasks using Presentation software (version 9.9; Neurobehavioral Systems, Inc).

fMRI PREPROCESSING

We used SPM5 software for preprocessing and statistical analysis of the imaging data (Wellcome Department of Cognitive Neurology). We excluded the first 5 images we acquired from our analysis to avoid any artifacts caused by the effects of magnetic saturation. We performed a spatial realignment on the remaining 448 images to correct for head motion. Normalization of the images was accomplished using an echo planar imaging template (Montreal Neurological Institute). The normalized images were smoothed using an isotropic gaussian kernel (8 mm full-width half-maximum).

STATISTICAL ANALYSIS

Our first statistical analysis of the preprocessed fMRI data was carried out on the individual level. In this analysis, we modeled the different conditions (salty high-calorie, sweet high-calorie, low-calorie, and neutral) as explanatory variables within the context of a general linear model. We mod-

eled the hemodynamic response as boxcar functions convolved with a synthetic hemodynamic response function. To assess differences in brain activation between obese participants and nonobese controls, we generated individual contrast images (contrasting food cues with neutral cues) for each individual and then included them in our second-level analyses. We used multiple regression analyses to assess group differences and the association between brain activity and both food-related and neutral cues. Moreover, this approach was also used to compute the influence of BMI and of leptin concentrations on cue reactivity. The statistical model included orthogonalized BMI and leptin concentration, weight group, an interaction regressor for the weight group × leptin interaction, as well as age and sex. Because the analyses were strongly hypothesis driven and anatomically localized to the ventral striatum, we applied the following familywise error correction method ($P < .05$). We defined the region of interest as the intersection of 2 a priori derived masks, that is, an anatomical mask for the ventral striatum and a mask for the main effect of the paradigm (food > neutral) built by an Statistical Parametric Mapping *t*-value map with a threshold of $P < .01$. We obtained our binary mask by retrieving a region of interest mask of the ventral striatum from the Brede database (<http://neuro.imm.dtu.dk/services/jerne/brede/>) and converting it to a binary mask with a threshold of $P > .25$. For exploratory whole-brain analysis, we performed a 1-sample *t* test of the obese and nonobese groups using a threshold of $P < .05$, familywise error corrected, with a minimum cluster size of $k = 10$ adjacent voxels.

For illustration purposes, we extracted the maximum parameter estimates from the individual contrast images in the ventral striatum and cross-correlated them with individual leptin concentrations using SPSS statistical software (version 16.0.2; SPSS, Inc).

Statistical differences in the demographic and behavioral data, as well as in the BMI and leptin concentrations, were likewise analyzed using SPSS software. To assess the association between group (obese vs nonobese participants) and subjective food cravings during the scanning session, as well as the duration of the food cravings, we conducted a repeated-measures analysis of variance, with food cravings as the dependent variable, group as the between-subjects factor, and time as the within-subject factor. We performed this analysis separately for the categories of food and neutral stimuli.

Table 1. Sample Characteristics, Leptin Concentration, and Craving Measures in 44 Participants

	Mean (SEM)			t Value	P Value
	Total	Obese	Nonobese		
Sex, F/M, No.	30/14	15/6	15/8		
Age, y	40.7 (12.2)	44.0 (12.7)	37.7 (11.4)	1.73	.67
Height, m	1.7 (0.9)	1.7 (0.9)	1.7 (0.1)	-1.56	.96
Weight, kg	95.1 (23.2)	105.2 (15.1)	66.6 (10.1)	9.86	<.001
Waist, cm	94.9 (22.8)	116.2 (12.1)	75.6 (7.8)	13.09	<.001
BMI	29.2 (8.6)	36.9 (5.7)	22.1 (1.6)	11.93	<.001
Leptin concentration, ng/mL	17.6 (15.4)	28.4 (14.4)	7.7 (7.6)	5.97	<.001
Craving					
Neutral cues	25.2 (19.8)	23.4 (23.7)	26.8 (15.7)	0.57	.57
Food cues	52.4 (22.3)	52.8 (27.2)	52.1 (17.4)	0.11	.92
Maximum	73.9 (24.1)	71.8 (29.6)	75.8 (18.1)	0.54	.60

Abbreviation: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared).

Table 2. Main Effect in Obese and Nonobese Participants

Side	Lobe	Brain Area ^a	Brodmann Area	Cluster Size, Voxels	MNI Coordinates			t _{max}
					x	y	z	
R/L	Occipital	Lingual gyrus, middle occipital gyrus, cuneus, calcarine, inferior occipital gyrus	17, 18, 19	5329	12	-90	-2	10.86
L	Frontal	Inferior frontal gyrus	47	52	-24	30	-14	6.61
L	Parietal	Superior parietal lobule	7	100	-26	-70	46	6.15
L	Limbic	Cingulate gyrus	23	10	0	-34	32	5.70

Abbreviations: L, left; MNI, Montreal Neurological Institute; R, right.

^aIndicates areas that showed a stronger blood oxygen level–dependent response to food cues compared with neutral cues in 44 obese patients and nonobese control subjects ($P < .05$, familywise error corrected; cluster size ≥ 10 voxels).

RESULTS

The mean (SEM) age of the sample was 40.7 (12.2) years, with no significant difference between the patients and controls ($P = .67$). The mean (SEM) BMI was 29.2 (8.6) for all participants (range, 18.2–47.5), and their mean leptin concentration was 17.6 (15.4) ng/mL (range, 0.6–57.2 ng/mL). Obese participants differed significantly from the nonobese individuals in terms of BMI ($t = 11.93$; $P < .001$) and leptin concentration ($t = 5.97$; $P < .001$). The mean score on the Fagerström Test for Nicotine Dependence for the 6 obese participants who smoked was 2.00 (2.53) and for the 7 smokers in the nonobese group was 2.71 (2.56) ($t = 2.80$; $P = .03$). **Table 1** provides a detailed look at the characteristics and leptin measurements of our sample. An exploratory, whole-brain fMRI analysis of the main effects of our cue reactivity paradigm showed clusters of brain activation in the visual and limbic regions (**Table 2** and **Figure 2**).

fMRI CUE REACTIVITY AND ITS ASSOCIATION WITH BMI

To test the effects of cue presentation on the reward system, we performed a hypothesis-driven analysis of striatal blood oxygen level–dependent (BOLD) response. We defined the region of interest as the intersection of the 2 a priori derived masks (see the “Statistical Analysis” subsection of the “Methods” section).

We found a positive correlation between individual BMI and food cue–induced activation of the ventral striatum (left ventral striatum, $t_{\max} = 4.17$; right ventral striatum, $t_{\max} = 5.44$; $P < .05$, familywise error corrected; **Table 3**).

Figure 3A presents a statistical parametric map to show the association between BMI and BOLD response in the ventral striatum ($P < .005$ uncorrected; cluster size ≥ 10 voxels). For illustration purposes, we used the extracted signal change of the data for correlation. **Figure 3B** presents a scatterplot of the correlation between BMI and BOLD response ($r = 0.47$; $P = .001$).

EFFECTS OF LEPTIN ON fMRI CUE REACTIVITY

As expected, we detected a positive correlation between plasma leptin concentration and BMI in our sample ($r = 0.46$; $P = .001$). The concentration of leptin in the plasma differed significantly between obese and nonobese participants (28.4 vs 7.6 ng/mL; $t = 5.97$; $P < .001$). Because other studies have suggested that leptin regulates body weight by affecting the hypothalamic and mesolimbic pathways, we tested the hypothesis that fMRI reactivity to food cues is associated with plasma leptin concentration. Our results showed a significant positive relationship between plasma leptin concentration and the BOLD signal in the right ventral striatum ($t_{\max} = 3.64$; $P < .05$, familywise error corrected; **Table 3**).

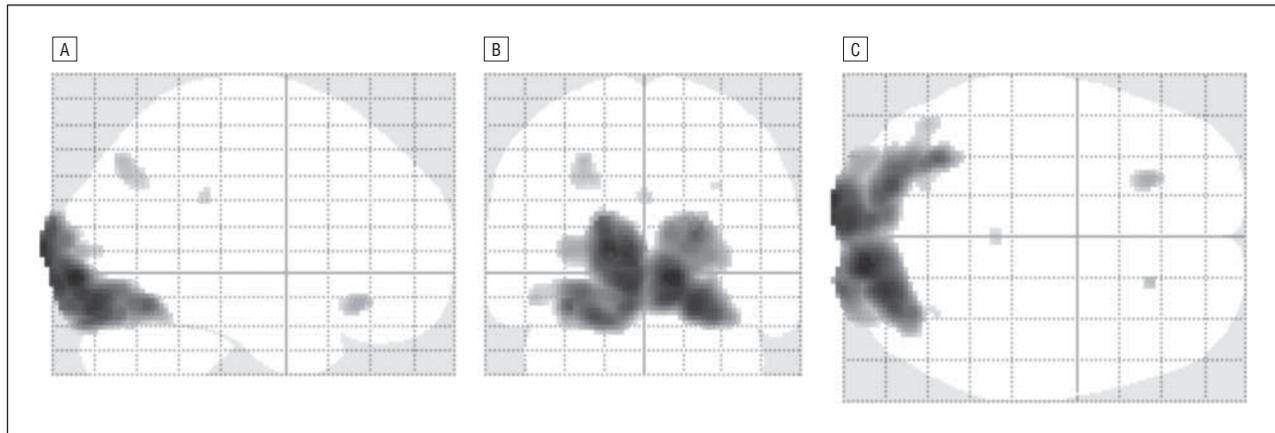


Figure 2. Maximum intensity projection showing the main effect in obese and nonobese participants (1-sample *t* test [N=44], $P < .05$, corrected for familywise error; cluster size ≥ 10 voxels). A, Sagittal view. B, Coronal view. C, Transverse view.

Table 3. Correlation of BMI and Leptin Plasma Concentration With Food Cue–Induced Striatal Brain Activation in 44 Participants^a

Side	Brain Area	Cluster Size, Voxels	MNI Coordinates			t_{max}
			x	y	z	
BMI						
L	Ventral striatum	39	-22	16	-6	4.17
R	Ventral striatum	59	24	10	-12	5.44
Leptin Plasma Concentration						
R	Ventral striatum	5	24	8	-10	3.64

Abbreviations: BMI, body mass index; L, left; MNI, Montreal Neurological Institute; R, right.

^aContrasting food cues vs neutral cues, $P < .05$, familywise error corrected.

Figure 3C shows the association between individual plasma leptin concentration and BOLD response in the ventral striatum ($P < .005$, uncorrected; cluster size ≥ 10 voxels). For illustration purposes, we used the extracted signal change to show the correlation between the BOLD response and the plasma leptin concentrations. Figure 3D illustrates the association between plasma leptin concentration and ventral striatal activation ($r = 0.27$; $P = .04$).

We found no association between weight group and plasma leptin concentrations. There also were no differences between food categories, most notably between the high- and low-calorie foods.

SUBJECTIVE FOOD CRAVINGS

We observed no significant difference between the groups in terms of their subjective food cravings, as assessed during the fMRI session following 6 hours of abstinence from food. The obese and nonobese participants both reported more food cravings after being presented with blocks of food-related stimuli than after viewing neutral blocks (mean [SEM] visual analog scale score, 52.4 [3.7] vs 25.2 [3.0]; $P < .001$, main effect of category). Both groups also reported a significant increase in food cravings over the course of the experiment during the neutral blocks (main effect of time, $P = .001$) and during the food blocks (main effect of time, $P = .003$). We found no interaction between group and block type (ie, food vs neu-

tral), indicating no difference in cue-induced food cravings between our obese and nonobese participants (Table 1).

COMMENT

The main finding of our study was a significant positive correlation between plasma leptin concentration and fMRI BOLD response in ventral striatal regions during the presentation of visual food cues. We also found BMI to be positively correlated with brain activation in the ventral striatum. On an exploratory level of analysis, various additional brain areas involved in visual, motivational, and gustatory processing were activated by food cues.

Previous evidence has suggested that the responsiveness of the mesolimbic reward system increases in response to visual food cues in the context of obesity. In a recent study, high-calorie food cues were demonstrated to have an effect on mesolimbic BOLD response in a sample of 13 obese women.¹⁶ Our data go beyond this observation by presenting evidence that BMI and food cue reactivity are associated: the higher an individual's BMI, the more mesolimbic activity followed the presentation of food cues. Moreover, evidence from a recently published fMRI study¹⁷ demonstrated that food addiction scores (as determined on the Yale Food Addiction Scale) correlated with an elevated BOLD signal in reward-associated structures (eg, the anterior cingulate, medial

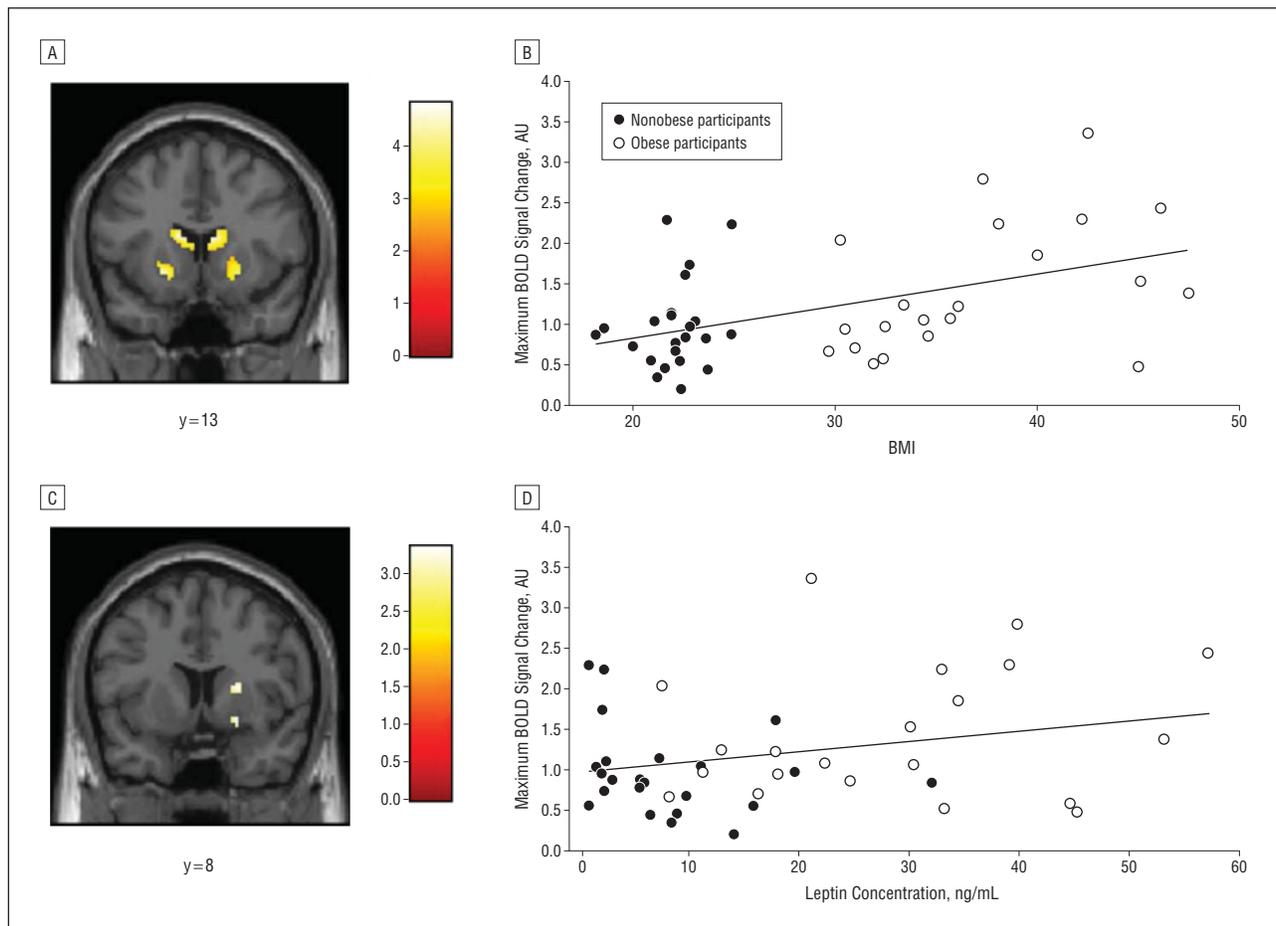


Figure 3. Blood oxygen level–dependent (BOLD) response in the ventral striatum. A, A statistical parametric map shows the association between BOLD response in the ventral striatum and body mass index (BMI; calculated as weight in kilograms divided by height in meters squared) ($P < .005$, uncorrected for illustration purposes; cluster size ≥ 10 voxels). B, A scatterplot further illustrates this positive correlation ($r = 0.47$; $P = .001$). C, A statistical parametric map shows the association between BOLD response in the ventral striatum and plasma leptin concentration ($P < .005$, uncorrected; cluster size ≥ 10 voxels). D, A scatterplot also illustrates this positive correlation ($r = 0.27$; $P = .04$). In the statistical parametric map, the color keys represent the t values; in the scatterplots, the solid lines represent the linear regression fit across all subjects. AU indicates arbitrary units.

orbitofrontal cortex, and amygdala) in response to visual food stimuli and correlated with reduced BOLD signals of inhibitory regions (eg, the lateral orbitofrontal cortex) in response to receipt of food.

Based on previous findings in drug addicts,³⁴⁻³⁶ it is possible that reduced dopamine D₂ receptor availability in the ventral striatum of obese individuals is at least partly responsible for this effect.¹⁵ Whether this reduced availability of dopamine D₂ receptors represents a downregulation of reward circuits^{12,37} following overstimulation remains to be elucidated. In the case of alcoholism, an inverse correlation has been demonstrated between mesolimbic D₂ receptor availability and cue reactivity,³⁴ suggesting that reduced basal activity might be accompanied by an increased sensitivity toward external stimulation.³⁸ Recent preclinical data using animal models support this hypothesis, showing that extended access to high-calorie foods causes downregulation of dopamine D₂ receptors in rats in addition to addictionlike reward deficits and the accompanying compulsive food-seeking behavior.³⁹

Our observations of the interaction between plasma leptin concentrations and fMRI cue reactivity constitute preliminary evidence that leptin plays a regulatory role

in the processing of food-related stimuli in obese individuals.

This finding expands on insights derived from studies performed on patients with a rare genetic defect leading to LDS. The study by Farooqi et al²⁹ found the presentation of visual food cues in 2 patients with LDS to be associated with increased striatal activation, which was neutralized by intravenous application of recombinant leptin. Furthermore, after leptin treatment, hunger decreased and satiety increased after meals and activation in striatal regions decreased. This decrease in activation was also found to be correlated with the subjects' prior ratings of the appeal of food pictures, albeit only when they were in the fasted state.

A second fMRI study²⁸ measured 3 subjects with LDS who had been undergoing leptin-substitution therapy for many years, before and after discontinuing their leptin treatment. After discontinuing leptin treatment, the patients showed increased visual food cue–induced signal change in regions linked to hunger (the insula and the parietal and temporal cortices) and decreased activity in frontal areas linked to inhibition (the prefrontal cortex).

In addition, further results in a magnetic resonance morphometry study⁴⁰ demonstrated in patients with LDS that

long-term leptin replacement therapy resulted in an increase of gray matter tissue in the frontal cortex, primarily in the left anterior cingulate gyrus. Gray matter tissue was also increased in the left inferior parietal lobule and the left cerebellum structures, which have been implicated in processing and regulating hunger and satiation.⁴¹

All these studies included only a few patients with the very rare LDS, but their results already suggest that leptin might exert its appetite-regulating effect at least in part by interacting with the mesolimbic pathways. A study in rodents demonstrated that a chronic reduction of leptin receptor activity in the VTA using short interfering RNA knockdown enhances sensitivity to highly palatable foods.²⁰ Moreover, rodents treated with a leptin antagonist and given access to a high-fat diet developed significantly greater hyperphagia and weight gain than did control rodents that were exposed to a high-fat diet without any additional treatment.⁴²

Notably, data from Farooqi et al,²⁹ which show that increased plasma leptin concentrations cause decreased striatal activation in LDS, stand in contrast to our results. We strongly believe that this fundamental divergence between our results originates in the different study populations. The obese participants recruited for our study had DIO, had high plasma concentrations of leptin, and likely had developed an acquired relative leptin resistance, whereas individuals with LDS, such as those in the study by Farooqi et al, had a congenital lack of leptin.

Research on elevated plasma leptin concentrations in DIO suggests that leptin may be ineffective in signaling satiety. For this reason, some have hypothesized that obese individuals with significantly increased leptin levels have become relatively resistant to the catabolic effect of leptin.⁴³

Although the DIO model is complex and because we lack definitive evidence showing which factors are responsible for the impairment of leptin's homeostatic effect, acquired leptin resistance appears to involve central (abnormalities on receptor and/or postreceptor signaling) or peripheral (abnormalities in transport across the blood-brain barrier) alterations to physiological mechanisms or both. (For more detailed insight into leptin resistance, see Scarpace and Zhang⁴⁴ and Meyers et al.⁴⁵)

Moreover, preclinical research with rodents has demonstrated that congenital leptin deficiency causes significant changes in leptin-sensitive hypothalamic neurons.⁴⁶ One can assume that similar changes, such as altered leptin-dependent synaptic plasticity in the VTA, occur in the brain morphologic features of individuals with LDS.

Physiologically, leptin binds to specific leptin receptors and activates Janus kinase 2, which subsequently phosphorylates signal transducers and transcription activators (STAT), in particular, STAT3. STAT3 activates the transcription of pro-opiomelanocortin, which mediates the effect of leptin on certain areas in the central nervous system.⁴⁷ For this reason, impaired STAT3 phosphorylation has been identified as one marker of cellular leptin resistance.⁴⁸

In rodents with DIO, the STAT3 phosphorylation of neuropeptide Y neurons, which are responsible for the anorexigenic effect of leptin, is dramatically diminished within the arcuate nucleus of the hypothalamus.⁴⁹

Additionally, a recently published study⁵⁰ on rats with DIO has identified the VTA as another specific region of cellular leptin resistance, as measured using reduced STAT3 phosphorylation. These data suggest that DIO-induced leptin-resistance diminishes the dopamine-reducing firing of leptin neurons from the VTA into the nucleus accumbens.

In addition to its effects on appetite regulation, leptin has been found to affect addictive behavior by increasing the reward value of external stimulation.²³ This hypothesis has been supported by preclinical and clinical data that have shown increased leptin activity to be associated with addictive behavior, craving, and reward expectation.^{24-27,51-53}

Although the approach is likely far too simplistic, we surmise, based on the preclinical research mentioned as well as our current findings, that an acquired impairment of the dopamine-reducing leptin effect in the nucleus accumbens combined with an acquired reduction of striatal D₂ receptors (caused by a high-calorie diet) might result in hyperreactivity of the mesolimbic system toward reward-predicting cues in obese subjects—similar to what we see in patients with addiction disorders. This might explain why obese individuals are unable to adapt their responsiveness to food cues and, consequently, their food intake according to their physiological needs.

We detected no significant group difference in subjective food cravings assessed during the fMRI session following 6 hours of food abstinence. Obese and non-obese participants reported more increased food craving after viewing food blocks than they did after viewing neutral blocks, and they reported a significant increase in food cravings during the course of the experiment in both the neutral and the food blocks. No interaction between group and category (food vs neutral) was found, indicating the absence of differences in cue-induced food cravings between obese and nonobese participants.

However, craving represents a subjective measure influenced by an unclear number of physiological as well as implicit and explicit cognitive factors; even in studies on alcohol and drug addiction, low construct validity has been a repeated complaint.^{54,55} In addition, Bartoshuk et al⁵⁶ demonstrated that the use of conventionally labeled scales (taste related) does not take into account that taste varies genetically (supertasters, weak tasters, and non-tasters), thereby rendering comparisons across taste groups based only such scales invalid. This could be one reason why we found no association between craving and fMRI cue reactivity in our study.

The correlation between plasma leptin concentration and striatal BOLD response to food cues does not necessarily imply causation. Furthermore, our region of interest was limited to the ventral striatum.

Given that smoking is associated with appetite and plasma leptin concentration,⁵⁷ our inclusion of smokers might represent another limitation of our study design. In addition, other eating-related hormones have been described as affecting the projection of dopamine from the VTA to the nucleus accumbens. The gastric-derived peptide ghrelin affects brain circuits involved in energy balance, stimulates accumbal dopamine release, and may increase the incentive value of food intake.⁵⁸ Moreover, there

is substantial evidence suggesting that the catabolic peptide insulin acts in the VTA to suppress dopaminergic transmission and hedonic feeding.⁵⁹ In our experiment, however, we focused solely on leptin and did not collect data concerning ghrelin or insulin.

These shortcomings notwithstanding, our data provide evidence that leptin plays a physiological role in modulating the responsivity of reward pathways to food cues and also suggest that the homeostatic feedback mechanism between leptin and mesolimbic reward function might be impaired in obese patients. To put this in perspective, we believe that by contributing to a better understanding of the impaired interaction between homeostatic and motivational pathways in obesity, these findings could help identify new entry points for the transfer of various psychotherapeutic and pharmaceutical interventions that have been successfully tested in addiction research to the treatment of obesity.

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REFERENCES

- Caballero B. The global epidemic of obesity: an overview. *Epidemiol Rev.* 2007; 29:1-5.
- Hyde R. Europe battles with obesity. *Lancet.* 2008;371(9631):2160-2161.
- Considine RV, Considine EL, Williams CJ, Hyde TM, Caro JF. The hypothalamic leptin receptor in humans: identification of incidental sequence polymorphisms and absence of the db/db mouse and fa/fa rat mutations. *Diabetes.* 1996;45(7):992-994.
- Tsai AG, Wadden TA. Systematic review: an evaluation of major commercial weight loss programs in the United States. *Ann Intern Med.* 2005;142(1):56-66.
- Haslam DW, James WP. Obesity. *Lancet.* 2005;366(9492):1197-1209.
- Hebebrand J, Fichter M, Gerber G, Görg T, Hermann H, Geller F, Schäfer H, Remschmidt H, Hinney A. Genetic predisposition to obesity in bulimia nervosa: a mutation screen of the melanocortin-4 receptor gene. *Mol Psychiatry.* 2002;7(6):647-651.
- Bell CG, Walley AJ, Froguel P. The genetics of human obesity. *Nat Rev Genet.* 2005;6(3):221-234.
- Hebebrand J, Hinney A. Environmental and genetic risk factors in obesity. *Child Adolesc Psychiatr Clin N Am.* 2009;18(1):83-94.
- Bassareo V, Di Chiara G. Differential responsiveness of dopamine transmission to food-stimuli in nucleus accumbens shell/core compartments. *Neuroscience.* 1999;89(3):637-641.
- Small DM, Jones-Gotman M, Dagher A. Feeding-induced dopamine release in dorsal striatum correlates with meal pleasantness ratings in healthy human volunteers. *Neuroimage.* 2003;19(4):1709-1715.
- Small DM, Zatorre RJ, Dagher A, Evans AC, Jones-Gotman M. Changes in brain activity related to eating chocolate: from pleasure to aversion. *Brain.* 2001; 124(pt 9):1720-1733.
- Volkow ND, Wang GJ, Fowler JS, Telang F. Overlapping neuronal circuits in addiction and obesity: evidence of systems pathology. *Philos Trans R Soc Lond B Biol Sci.* 2008;363(1507):3191-3200.
- Volkow ND, Wise RA. How can drug addiction help us understand obesity? *Nat Neurosci.* 2005;8(5):555-560.
- Fulton S. Appetite and reward. *Front Neuroendocrinol.* 2010;31(1):85-103.
- Wang GJ, Volkow ND, Logan J, Pappas NR, Wong CT, Zhu W, Netusil N, Fowler JS. Brain dopamine and obesity. *Lancet.* 2001;357(9253):354-357.
- Rothmund Y, Preuschhof C, Bohner G, Bauknecht HC, Klingebiel R, Flor H, Klapp BF. Differential activation of the dorsal striatum by high-calorie visual food stimuli in obese individuals. *Neuroimage.* 2007;37(2):410-421.
- Gearhardt AN, Yokum S, Orr PT, Stice E, Corbin WR, Brownell KD. Neural correlates of food addiction. *Arch Gen Psychiatry.* 2011;68(8):808-816.
- Friedman JM, Halaas JL. Leptin and the regulation of body weight in mammals. *Nature.* 1998;395(6704):763-770.
- Figlewicz DP, Evans SB, Murphy J, Hoen M, Baskin DG. Expression of receptors for insulin and leptin in the ventral tegmental area/substantia nigra (VTA/SN) of the rat. *Brain Res.* 2003;964(1):107-115.
- Hommel JD, Trinko R, Sears RM, Georgescu D, Liu ZW, Gao XB, Thurmon JJ, Marinelli M, DiLeone RJ. Leptin receptor signaling in midbrain dopamine neurons regulates feeding. *Neuron.* 2006;51(6):801-810.
- Fulton S, Pissios P, Manchon RP, Stiles L, Frank L, Pothos EN, Maratos-Flier E, Flier JS. Leptin regulation of the mesoaccumbens dopamine pathway. *Neuron.* 2006;51(6):811-822.
- Palmiter RD. Is dopamine a physiologically relevant mediator of feeding behavior? *Trends Neurosci.* 2007;30(8):375-381.
- Fulton S, Woodside B, Shizgal P. Modulation of brain reward circuitry by leptin. *Science.* 2000;287(5450):125-128.
- Kiefer F, Jahn H, Kellner M, Naber D, Wiedemann K. Leptin as a possible modulator of craving for alcohol. *Arch Gen Psychiatry.* 2001;58(5):509-510.
- Kiefer F, Jahn H, Wolf K, Kämpf P, Knautd K, Wiedemann K. Free-choice alcohol consumption in mice after application of the appetite regulating peptide leptin. *Alcohol Clin Exp Res.* 2001;25(5):787-789.
- Kiefer F, Jahn H, Jaschinski M, Holzbach R, Wolf K, Naber D, Wiedemann K. Leptin: a modulator of alcohol craving? *Biol Psychiatry.* 2001;49(9):782-787.
- von der Goltz C, Koopmann A, Dinter C, Richter A, Rockenbach C, Grosshans M, Nakovics H, Wiedemann K, Mann K, Winterer G, Kiefer F. Orexin and leptin are associated with nicotine craving: a link between smoking, appetite and reward. *Psychoneuroendocrinology.* 2010;35(4):570-577.
- Baicy K, London ED, Monterosso J, Wong ML, Delibasi T, Sharma A, Licinio J. Leptin replacement alters brain response to food cues in genetically leptin-deficient adults. *Proc Natl Acad Sci U S A.* 2007;104(46):18276-18279.
- Farooqi IS, Bullmore E, Keogh J, Gillard J, O'Rahilly S, Fletcher PC. Leptin regulates striatal regions and human eating behavior. *Science.* 2007;317(5843): 1355. doi:10.1126/science.1144599.
- Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. *Arch Gen Psychiatry.* 1961;4:561-571.
- Heatherton TF, Kozlowski LT, Frecker RC, Fagerström KO. The Fagerström Test for Nicotine Dependence: a revision of the Fagerström Tolerance Questionnaire. *Br J Addict.* 1991;86(9):1119-1127.
- Stunkard AJ, Messick S. The three-factor eating questionnaire to measure dietary restraint, disinhibition and hunger. *J Psychosom Res.* 1985;29(1):71-83.
- Lang PJ, Bradley MM, Cuthbert BN. *The International Affective Picture System (IAPS)*. Gainesville: Center for Research in Psychophysiology, University of Florida; 1999.
- Heinz A, Siessmeier T, Wrase J, Hermann D, Klein S, Grüsser SM, Flor H, Braus DF, Buchholz HG, Gründer G, Schreckenberger M, Smolka MN, Rösch F, Mann K, Bartenstein P. Correlation between dopamine D₂ receptors in the ventral striatum and central processing of alcohol cues and craving [published correction appears in *Am J Psychiatry.* 2004;161(12):2344]. *Am J Psychiatry.* 2004;161(10):1783-1789.
- Volkow ND, Chang L, Wang GJ, Fowler JS, Ding YS, Sedler M, Logan J, Franceschi D, Gatley J, Hitzemann R, Gifford A, Wong C, Pappas N. Low level of brain dopamine D₂ receptors in methamphetamine abusers: association with metabolism in the orbitofrontal cortex. *Am J Psychiatry.* 2001;158(12):2015-2021.
- Volkow ND, Fowler JS, Wang GJ, Hitzemann R, Logan J, Schlyer DJ, Dewey SL, Wolf AP. Decreased dopamine D₂ receptor availability is associated with reduced frontal metabolism in cocaine abusers. *Synapse.* 1993;14(2):169-177.
- Comings DE, Blum K. Reward deficiency syndrome: genetic aspects of behavioral disorders. *Prog Brain Res.* 2000;126:325-341.
- Wang GJ, Volkow ND, Fowler JS. The role of dopamine in motivation for food in humans: implications for obesity. *Expert Opin Ther Targets.* 2002;6(5):601-609.
- Johnson PM, Kenny PJ. Dopamine D₂ receptors in addiction-like reward dysfunction and compulsive eating in obese rats. *Nat Neurosci.* 2010;13(5):635-641.
- Matochik JA, London ED, Yildiz BO, Ozata M, Caglayan S, DePaoli AM, Wong ML, Licinio J. Effect of leptin replacement on brain structure in genetically leptin-deficient adults. *J Clin Endocrinol Metab.* 2005;90(5):2851-2854.
- Tataranni PA, Gautier JF, Chen K, Uecker A, Bandy D, Salbe AD, Pratley RE, Lawson M, Reiman EM, Ravussin E. Neuroanatomical correlates of hunger and satiation in humans using positron emission tomography. *Proc Natl Acad Sci U S A.* 1999;96(8):4569-4574.

42. Zhang J, Matheny MK, Tümer N, Mitchell MK, Scarpace PJ. Leptin antagonist reveals that the normalization of caloric intake and the thermic effect of food after high-fat feeding are leptin dependent. *Am J Physiol Regul Integr Comp Physiol*. 2007;292(2):R868-R874.
43. Heymsfield SB, Greenberg AS, Fujioka K, Dixon RM, Kushner R, Hunt T, Lubina JA, Patane J, Self B, Hunt P, McCamish M. Recombinant leptin for weight loss in obese and lean adults: a randomized, controlled, dose-escalation trial. *JAMA*. 1999;282(16):1568-1575.
44. Scarpace PJ, Zhang Y. Leptin resistance: a predisposing factor for diet-induced obesity. *Am J Physiol Regul Integr Comp Physiol*. 2009;296(3):R493-R500.
45. Myers MG, Cowley MA, Münzberg H. Mechanisms of leptin action and leptin resistance. *Annu Rev Physiol*. 2008;70:537-556.
46. Bouret SG, Draper SJ, Simerly RB. Trophic action of leptin on hypothalamic neurons that regulate feeding. *Science*. 2004;304(5667):108-110.
47. Enriori PJ, Evans AE, Sinnayah P, Jobst EE, Tonelli-Lemos L, Billes SK, Glavas MM, Grayson BE, Perello M, Nilini EA, Grove KL, Cowley MA. Diet-induced obesity causes severe but reversible leptin resistance in arcuate melanocortin neurons. *Cell Metab*. 2007;5(3):181-194.
48. El-Haschimi K, Pierroz DD, Hileman SM, Bjørbaek C, Flier JS. Two defects contribute to hypothalamic leptin resistance in mice with diet-induced obesity. *J Clin Invest*. 2000;105(12):1827-1832.
49. Münzberg H, Flier JS, Bjørbaek C. Region-specific leptin resistance within the hypothalamus of diet-induced obese mice. *Endocrinology*. 2004;145(11):4880-4889.
50. Matheny M, Shapiro A, Tümer N, Scarpace PJ. Region-specific diet-induced and leptin-induced cellular leptin resistance includes the ventral tegmental area in rats. *Neuropharmacology*. 2011;60(2-3):480-487.
51. Blednov YA, Walker D, Harris RA. Blockade of the leptin-sensitive pathway markedly reduces alcohol consumption in mice. *Alcohol Clin Exp Res*. 2004;28(11):1683-1692.
52. Kiefer F, Jahn H, Otte C, Demiralay C, Wolf K, Wiedemann K. Increasing leptin precedes craving and relapse during pharmacological abstinence maintenance treatment of alcoholism. *J Psychiatr Res*. 2005;39(5):545-551.
53. Hillemecher T, Bleich S, Frieling H, Schanze A, Wilhelm J, Sperling W, Kornhuber J, Kraus T. Evidence of an association of leptin serum levels and craving in alcohol dependence. *Psychoneuroendocrinology*. 2007;32(1):87-90.
54. Myrick H, Anton RF, Li X, Henderson S, Drobos D, Voronin K, George MS. Differential brain activity in alcoholics and social drinkers to alcohol cues: relationship to craving. *Neuropsychopharmacology*. 2004;29(2):393-402.
55. Grüsser SM, Wrase J, Klein S, Hermann D, Smolka MN, Ruf M, Weber-Fahr W, Flor H, Mann K, Braus DF, Heinz A. Cue-induced activation of the striatum and medial prefrontal cortex is associated with subsequent relapse in abstinent alcoholics. *Psychopharmacology (Berl)*. 2004;175(3):296-302.
56. Bartoshuk LM, Duffy VB, Green BG, Hoffman HJ, Ko CW, Lucchina LA, Marks LE, Snyder DJ, Weiffenbach JM. Valid across-group comparisons with labeled scales: the gLMS versus magnitude matching. *Physiol Behav*. 2004;82(1):109-114.
57. Koopmann A, Dinter C, Grosshans M, von der Goltz C, Hentschel R, Dahmen N, Gallinat J, Wagner M, Gründer G, Thürauf N, Wienker T, Brinkmeyer J, Mobscher A, Spreckelmeyer KN, Clepce M, de Millas W, Wiedemann K, Winterer G, Kiefer F. Psychological and hormonal features of smokers at risk to gain weight after smoking cessation—results of a multicenter study. *Horm Behav*. 2011;60(1):58-64.
58. Landgren S, Simms JA, Thelle DS, Strandhagen E, Bartlett SE, Engel JA, Jerlhag E. The ghrelin signalling system is involved in the consumption of sweets. *PLoS One*. 2011;6(3):e18170. doi:10.1371/journal.pone.0018170.
59. Bruijnzeel AW, Corrie LW, Rogers JA, Yamada H. Effects of insulin and leptin in the ventral tegmental area and arcuate hypothalamic nucleus on food intake and brain reward function in female rats. *Behav Brain Res*. 2011;219(2):254-264.