(Still) Longing for Food: Insulin Reactivity Modulates Response to Food Pictures

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Abstract: Overweight and obesity pose serious challenges to public health and are promoted by our food-rich environment. We used functional magnetic resonance imaging (fMRI) to investigate reactivity to food cues after overnight fasting and following a standardized caloric intake (i.e., a 75 g oral glucose tolerance test, OGTT) in 26 participants (body mass index, BMI between 18.5 and 24.9 kg m⁻²). They viewed pictures of palatable food and low-level control stimuli in a block design and rated their current appetite after each block. Compared to control pictures, food pictures activated a large bilateral network typically involved in homeostatically and hedonically motivated food processing. Glucose ingestion was followed by decreased activation in the basal ganglia and paralimbic regions and increased activation in parietal and occipital regions. Plasma level increases in insulin correlated with cue-induced appetite at the neural and behavioral level. High insulin increases were associated with reduced activation in various bilateral regions including the fusiform gyrus, the superior temporal gyrus, the medial frontal gyrus, and the limbic system in the right hemisphere. In addition, they were accompanied by lower subjective appetite ratings following food pictures and modulated the neural response associated with it (e.g., in the fusiform gyrus). We conclude that individual insulin reactivity is critical to reduce food-cue responsiveness after an initial energy intake and thereby may help to counteract overeating. *Hum Brain Mapp* 34:2367–2380, 2013. © 2012 Wiley Periodicals, Inc.

Key words: appetite; insulin; oral glucose tolerance test; food processing; fMRI

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INTRODUCTION

Extensive availability of high energy-dense food and low levels of regular physical activities characterize many environments in the developed countries today. As a result, excess body weight rates tripled in the last two decades and include now roughly half of the adult population [e.g., for Europe, see Branca et al., 2007]. Therefore, tackling overweight and obesity is arguably “one of the most serious public health challenges in the 21st century” [p. 1, Branca et al., 2007] regarding the well-documented negative effects on health outcomes [Must et al., 1999]. However, little is known about the interplay of hormonal and neural mechanisms of appetite regulation, which complicates the task to derive empirically sound interventions. To bridge this gap, we investigated how a standardized caloric intake altered blood plasma levels of glucose and insulin and how these changes translate to the neural and behavioral response to pictures of palatable food.

Cognitive and Neural Mechanisms of Food Consumption

Mechanisms of food consumption are often described in terms of homeostatic regulatory circuits. Hunger is the primary motivational state which encourages food intake as a means of return to the individual state of equilibrium. A distinction between homeostatic and hedonic mechanisms is now well established [cf., Stroebe et al., 2008; Berridge, 2009] though there remain several objections regarding the feasibility and benefit of an experimental distinction at least for human participants [cf., Havermans, 2011]. Most early theories of food consumption focused on homeostatic hunger, which is experienced after a prolonged absence of energy intake. In contrast, hedonic hunger may persist even after subjective satiety is reached because it is driven by the availability of palatable food and its hedonic qualities such as taste [Lowe and Butryn, 2007]. Consequently, homeostatic hunger is largely independent of the food environment whereas hedonic hunger is stimulus-driven per definitionem. In a similar vein, Berridge [1996, 2009] proposed the term “wanting” as a shorthand for incentive salience, or the motivation (craving) to obtain a certain object. The term “liking” refers to the hedonic qualities of the object and both components are needed to experience full reward [cf., Berridge, 2009]. The concepts of Lowe and Butryn [2007] and Berridge [1996, 2009] are not synonymous, nevertheless, because liking does not depend on the environment, whereas wanting is substantially induced by food cues and often measured using instrumental behavior.

There is reason to believe that food consumption is substantially stimulated by hedonic aspects in affluent societies because the state of energy deprivation is seldom experienced prior to eating [Lowe and Butryn, 2007]. Hedonic aspects critically modulate the motivation toward food and feed mechanisms of sensitization and condition-

ing. But there is a risk that these processes lead to maladaptive solutions, similar to addictive behavior, consequently supporting excessive food consumption and, ultimately, obesity [Lutter and Nestler, 2009; Stroebe et al., 2008].

Whereas the importance of hedonic qualities in these processes is now widely acknowledged, its neurobiological basis is still to be explored in detail [Neary and Batterham, 2010]. To target hedonic aspects of appetite, a common procedure in fMRI experiments is to present pictures of palatable food to investigate food-cue reactivity [e.g., Fuhrer et al., 2008; Killgore and Yurgelun-Todd, 2005; Porubska et al., 2006; Simmons et al., 2005]. These studies provide converging evidence that a temporo-insulo-opercular and orbitofrontal network is critical in processing of food stimuli [Kringelbach, 2004; Porubska et al., 2006; van der Laan et al., 2011]. Additional brain regions are reliably involved in homeostatic hunger and energy-dependent processing, notably the hypothalamus and other limbic and paralimbic areas [cf., van der Laan et al., 2011; also see Fuhrer et al., 2008; LaBar et al., 2001; Morris and Dolan, 2001; Tataranni et al., 1999].

Not surprisingly, homeostatic hunger modulates the neural hedonic response itself [LaBar et al., 2001; Siep et al., 2009; Stockburger et al., 2009] increasing food-cue reactivity. There are different strategies to experimentally manipulate the impact of homeostatic hunger on hedonic aspects of food processing. The common design is to predefine a fasting period to investigate participants in a state of homeostatic hunger first. Then, a controlled amount of calories is administered using a standardized meal or a glucose solution. The glucose solution has the advantage of being more independent from context and individual factors such as palatability [Mela, 2001; Yeomans et al., 2004]. Orally administered glucose reliably enhances plasma levels of glucose and insulin and the response to it is indicative of insulin sensitivity [Matsuda and DeFronzo, 1999] and predicts long-term body weight change in non-diabetic participants with higher glucose reactivity protecting against weight gain [Pannacciulli et al., 2007]. Moreover, it has been demonstrated to modulate the BOLD signal of the hypothalamus [Liu et al., 2000; Smeets et al., 2005] in a dose-dependent relationship [Smeets et al., 2007].

Endocrinological Mechanisms of Food Consumption

Body weight regulation is arguably a complex physiological process involving exteroceptive and interoceptive information that are transcoded in interacting neural and endocrinological systems [Langhans and Geary, 2010]. For the present study, we focus on insulin that has been hypothesized as a major adiposity signal for >40 years [cf., Hillebrand and Geary, 2010]. Insulin receptors are widely distributed throughout most body tissues (e.g.,

liver and muscle) and insulin is actively transported via the blood-brain barrier to the brain [Woods et al., 2003] where insulin receptors are prominently expressed [e.g., in the hypothalamus, Hopkins and Williams, 1997]. In rodents, a knock-out of brain insulin-receptors leads to insulin resistance and hyperphagia [Bruning et al., 2000]. Especially the hypothalamus is critical in that process [Obici et al., 2002a,b].

Fasting insulin levels and insulin responses to glucose are associated with obesity and weight regulation [e.g., Bagdade et al., 1967; Slabber et al., 1994]. Schwartz et al. [1995] reported that insulin secretion in response to a meal and an OGTT was negatively associated with weight change during the following 3 years. However, there is evidence from experimental studies with rodents suggesting that insulin does not truly signal adiposity because after a period of forced feeding, insulin levels are more quickly restored to baseline than adipose-tissue mass [Hill-ebbrand and Geary, 2010]. Thus, insulin seems to serve as an early indicator to initiate change in food consumption, for example via meal termination [Vanderweele, 1994], by reducing the rewarding properties of food [cf. Figlewicz, 2003; Figlewicz and Benoit, 2009]. In humans, obesity was hypothesized to be associated with reduced cortical insulin sensitivity [cf., Pliquet et al., 2006; Tschritter et al., 2006]. To summarize, substantial empirical evidence suggests that insulin responsivity is essentially involved in controlling body weight but the exact mechanisms how insulin acts, especially on a neural basis, are still largely speculative.

Hypotheses

The aim of the study was to combine important facets of current knowledge into one comprehensive design to investigate the neural response to food cues, including the influence of homeostatic hunger and blood plasma levels of glucose and insulin on food-cue reactivity. To this end, participants viewed food and control pictures in a block design and indicated their current appetite after each block throughout the experiment. This was done once in a state of homeostatic hunger (i.e., ~ 12 h overnight fast) and once after the administration of a standardized caloric intake intended to reduce appetite.

We hypothesized that food pictures would increase subjective appetite compared to control pictures (main effect of food cues) and that the administration of glucose would lead to a reduction of appetite (main effect of the caloric intake). Food pictures compared to control pictures were expected to activate the whole hunger network (i.e., both homeostatic and hedonic networks) and the administration of glucose was expected to lead to decreased activation of the homeostatic-hunger network. Because hedonic aspects (referred to by the concepts of hedonic hunger and liking) are operationalized by the same manipulation (food-cue reactivity paradigm) in this study, we will refer to it using the more technical terms food-cue reactivity on the neural

and cue-induced appetite on the behavioral level. Notably, our design is not focused on the (controversial) distinction of homeostatic and hedonic processes, but on their interplay and their relation to insulin and glucose increases.

As a primary hypothesis, we expected that high increases of insulin levels would lead to stronger decreases of (i.e., covary negatively with) cue-induced appetite and food-related brain activation in these networks. As a secondary hypothesis, we expected that high increases of glucose levels following the OGTT would lead to stronger decreases of subjective appetite and food-related brain activation in hunger networks, over and above insulin, as well.

MATERIALS AND METHODS

Participants

Initially, 30 volunteers (mainly undergraduates) were successfully recruited for the experiment using flyers at the Faculty of Medicine, Mannheim, Germany. However, four participants had to be excluded for the following reasons: out of the predefined BMI range at the fMRI-scan date, nausea, severe head motion artifacts, and defective blood samples. This led to a sample of 26 right-handed volunteers (13 male) for the following analyses. Their mean age was 24.4 ± 3.4 years and they only were included in the study if their BMI was between 18.5 and 24.9 kg m^{-2} (i.e., within the range of normal weight). Participants spanned the whole predefined BMI range with a mean of $21.1 \pm 2.0 \text{ kg m}^{-2}$. They had no history of brain injury, reported no substance intake (verified by urine testing for illicit drug use, breath alcohol testing, and carbon monoxide measurements), were not under psychotropic medication, and suffered from no axis-I psychiatric disorder as assessed using the Mini-DIPS [Markgraf, 1994]. In addition, they were only included if they reported to be lifetime nonsmokers (i.e., having consumed less than a total of 20 cigarettes). Because the stimulus material included pictures of meals containing meat, vegetarians were not included. A urine pregnancy test was performed in all female participants and they participated before the 21st day of their menstrual cycle. Participants were scanned at the Central Institute of Mental Health. The study was approved by the institutional review boards of the Faculty of Medicine Mannheim of the Heidelberg University. Informed consent was obtained from all participants prior to taking part in the experiment.

Stimulus Material

The stimulus set used in this study consisted of 120 food pictures and 120 low-level control pictures (i.e., 60 per run). Food stimuli included pictures of warm and cold meals, desserts, fruits, and vegetables (see Fig. 1) and were selected based on high-palatability ratings in a web-based evaluation study. Control pictures were created by scrambling the food pictures to match in intensity, contrast, and

Figure 1.

Schematic summary of the fMRI block design. Note that verbal labels are translated. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

brightness. Pictures were presented via MR-compatible goggles using MRI Audio/Video Systems (Resonance Technology, Northridge, CA) simulating a viewing distance of 100 cm. Presentation® software (Version 9.90, Neurobehavioral Systems, Albany, CA) was used to present pictures and collect data.

Procedure

The design was developed focusing on food-cue reactivity of participants in a state of high (Run 1) and, induced by the preceding administration of the glucose solution, during the transition to a state of low homeostatic hunger (Run 2). Thus, participants had to be in a fasting state when arriving at the study center. They were allowed to take the last meal at 10 pm the day before. All participants were investigated in the morning and arrived between 7:30 and 9:00 am. They were sized and weighed. Their urine was tested for cannabis, opiates, cocaine, benzodiazepines, methamphetamines, and amphetamines. In addition, alcohol and CO content in breath were measured to verify abstinence from alcohol and tobacco. Approximately 10 min after their arrival, the first blood sample was collected. Then, participants either received a nicotine gum (Nicorette® Gum, 2 mg) or a placebo gum (Placebo Nicorette® Gum) according to a double-blinded, randomized crossover design as part of another study. They chewed the gum for 30 min and the second blood sample was taken subsequently. Thereafter, the fMRI experiment started. We will restrict our analysis to the placebo sessions only. Session effects were explored but were not significant.

Pictures of both categories were presented in a block design with food- and control blocks in a pseudorandom order to ensure that three blocks in a row never contained the same stimulus category. Each block consisted of five pictures. Every picture was presented for 4 s. After presenting the last picture of a block, a fixation cross appeared for 500 ms. Then, a rating slide with the statement: “I feel like eating now” was presented. Participants had to indicate how much they felt like eating at the moment on a visual analog scale with the end points: “totally disagree” versus “totally agree” by moving the joystick with their right hand. Values correspond to mm distance to the origin of the visual analog scale and the cursor was initially placed at the middle. After the response, “thank you” or, in case no rating was recorded for 10 s, “invalid rating” was shown as feedback for 1 s. Rating labels were presented in German. Then, a fixation cross followed and after a total time of 15.5 s, a new block started. After 12 blocks of each category, there was a short break to sample blood and to apply an OGTT. Participants drank a solution containing the equivalent of 75 g of glucose (defined by a 300 ml mixture of mono- and oligo-saccharides; ACCU-CHEK® Dextro® O.G-T., Roche) sitting on the scanner bed. The OGTT was administered to measure insulin secretion elicited by a standardized caloric intake to test central nervous regulation of appetite. Five minutes after they started drinking the glucose solution, participants continued with the second fMRI run, which consisted of new pictures presented in the same design. Thus, the second scan was supposed to accompany the highly dynamic transition from high to low homeostatic

hunger mimicking usual meal termination that is triggered 10–20 min following caloric intake. After completion, participants were seated and four more blood samples were drawn in 30 min time intervals outside the scanner. Participants returned for a second scan date ~ 9 days thereafter completing the same design with the other condition of placebo or nicotine to complete the crossover design.

Sample Treatment and Hormone Measurements

Blood samples were drawn into devices pretreated with EDTA and aprotinin (2000 kallikrein-inhibiting units per 7 ml of blood, Bayer, Leverkusen, Germany). The blood was chilled on ice immediately, spun at 1,500 g and 4°C within 60 min, and the plasma was frozen at -80°C. Insulin was measured by chemoluminescence immune assay (DiaSorin, Saluggia, Italy). The lower limit of detection was 0.61 $\mu\text{IU ml}^{-1}$. The intraassay coefficients of variation were 1.8 and 3.9% at concentrations of 45 and 120 $\mu\text{IU ml}^{-1}$, respectively. Interassay coefficients of variation at these concentrations were below 6.3% and below 2.6%, respectively. Crossreactivity with related peptides measured at 200 ng ml^{-1} were negligible for human c-peptide, proinsulin, and glucagon and was 2.9% for insulin-like growth factor I. Glucose was assayed photometrically with the hexokinase method on a Beckman-Coulter DxC800 device (Krefeld, Germany) at a lower detection limit of 0.3 mmol l^{-1} . Interassay coefficients of variation were below 2.6%.

Data Acquisition and Analysis

Images were acquired with a 3 Tesla whole-body MRI scanner (TRIO; Siemens, Erlangen, Germany) equipped with a standard head coil. The participants' head was stabilized using two additional small pillows that belong to the scanner equipment. Gradient-echo planar imaging (EPI) with a repetition time (TR) of 2,410 ms, an echo time (TE) of 25 ms and a flip angle of 80° was used for functional imaging. During both runs, 364 whole brain scans were acquired, each consisting of 42 transversal slices (2-mm thick, 1-mm gap), tilted axially parallel to the anterior commissure–posterior commissure line with 30° (192 mm field of view, FOV, 64 × 64 matrix size, 3 × 3 × 2 mm^3 voxel size). Additionally, a T1-weighted anatomical 3D magnetization-prepared rapid gradient echo dataset was acquired (TR = 1,900 ms, TE = 2.26 ms, FOV = 256, 176 slices, 1 × 1 × 1 mm^3 voxel size, flip angle = 9°) to check for structural irregularities.

Preprocessing and statistical analyses of brain imaging data were performed using SPM5 (Wellcome Department of Cognitive Neurology, London, UK). The first five scans were excluded from the analyses to avoid artifacts due to magnetic saturation effects. The remaining 359 scans were spatially realigned to correct for head motion over the course of the session and then normalized to an MNI (Montreal Neurological Institute, Quebec, Canada) EPI

template, resampled with 2 × 2 × 2 mm^3 voxels. Subsequent smoothing was done using an isotropic Gaussian kernel for group analysis (8 mm FWHM). The data were high-pass filtered at 128 s.

First-level analysis was performed by modeling the durations of picture category (food vs. control), run (pre- and postglucose administration), onsets of appetite rating, and the rating error (i.e., no rating recorded), if applicable, as explanatory variables within the context of the general linear model (GLM). Individual contrast images were computed to separately estimate the differences between food and control pictures for each run and for each participant.

These images were entered into a second-level analysis comprising a repeated measures ANCOVA. The model consisted of the two-level within-subject factor homeostatic hunger (food vs. control before and food vs. control after glucose administration) and four covariates reflecting between-subject differences (baseline glucose levels, baseline insulin levels, glucose reactivity, and insulin reactivity). Notably, these covariates were not significantly pairwise correlated ($|r| \leq 0.28$; $P > 0.15$). The baseline levels were modeled as covariates to account for initial interindividual differences. Using this model, we were able to test the food-cue reactivity (food vs. control pictures), the effect of the glucose administration on food-cue reactivity, and the interaction between food-cue reactivity and glucose administration with respect to individual hormonal reactivity. As outlined in the introduction, we focus on insulin as the prime candidate for a postprandial endocrinological indicator to reduce food-cue reactivity. We report additional analyses concerning glucose reactivity and the subjective appetite ratings in the Supporting Information. Session number, sex, BMI, and cognitive restraint (measured using the first factor of the German version of the three-factor eating questionnaire, Fragebogen zum Essverhalten, Pudel, and Westenhofer, 1989) were explored as further confounding covariates but because results remained essentially unchanged, we report the more parsimonious model.

Statistical thresholding is supposed to be guided by considerations of Type I and II errors given an estimated effect size [Cohen, 1992; Zarahn and Slifstein, 2001]. We expected a large effect of picture category (food vs. control) and therefore decided to use a more conservative threshold, that is an FDR-corrected $P < 0.001$ with a minimal cluster size of $k = 20$. Because pre-post- and interaction effects are usually less strong, activations exceeding an uncorrected threshold of $P < 0.001$ with a minimal cluster size of $k = 20$ (which corresponded well to the expected cluster size by chance of 17.6 voxels as computed by SPM) were considered as significant. This has been argued to be a reasonable compromise between reporting truly informative activations on the one hand and enabling the assessment of converging evidence by metaanalytic techniques on the other [cf., Lieberman and Cunningham, 2009]. Behavioral and hormonal data were analyzed using the statistical software package PASW (version 17.0, SPSS, Chicago, IL). For correlational analyses, mean subjective

appetite ratings were averaged over blocks within each condition (food vs. control pictures; pre vs. post OGTT) for every participant. To illustrate the association of insulin increases with the change in food-cue reactivity, we extracted the mean signal from anatomical masks of the fusiform gyrus, the orbitofrontal cortex and the ventral striatum (for details, see Supporting Information).

RESULTS

Subjective Appetite Ratings

We compared the effect of food versus control pictures, the effect of glucose administration, and their interaction on subjective appetite ratings using repeated measures ANOVA. Participants indicated higher appetite after viewing food compared with control pictures, $F(1, 25) = 36.4$, $P < 0.001$, $\eta_p^2 = 0.593$, demonstrating the main effect of food pictures (see Fig. 2). Mean appetite ratings decreased after glucose administration, $F(1, 25) = 20.2$, $P < 0.001$, $\eta_p^2 = 0.447$, demonstrating the main effect of the standardized caloric intake. In addition, there was a significant interaction between these two factors, that is ratings decreased more strongly after glucose administration when participants saw food pictures compared to control pictures, $F(1, 25) = 8.2$, $P = 0.008$, $\eta_p^2 = 0.249$. The mean rating duration was $3177.2 (\pm 998.6)$ ms. After the administration of glucose, there was a significant decrease in rating duration for control pictures, $t(25) = 2.70$, $P = 0.012$, but not for food pictures, $t(25) = 0.04$, $P = 0.97$. The interaction term of a repeated measures ANOVA for rating duration was

Figure 2.

Mean subjective appetite ratings ("I feel like eating now") following food pictures and control pictures before (pre) and after (post) the administration of glucose (error bars indicate ± 1 SD). Values correspond to mm distance to the origin of the visual analog scale.

Figure 3.

Time course for blood plasma concentrations of glucose (black) and insulin (gray) with respect to the OGTT at time point 0 (error bars indicate ± 1 SD).

significant as well, $F(1,25) = 11.93$, $P = 0.003$, indicating that the decrease was significantly stronger for control than for food pictures. Mean differences between male and female participants in appetite ratings and rating duration were explored but were not significant ($P > 0.2$).

Hormonal Results

As for the behavioral data, hormone trends were analyzed using separate repeated measures ANOVAs with the factor time consisting of the seven measurements for plasma levels of glucose and insulin, respectively. Huynh-Feldt correction was applied to correct for violations of sphericity. After glucose administration, there were significant increases of plasma glucose, $F(2.86, 61.10) = 33.1$, $P < 0.001$, $\eta_p^2 = 0.569$, and plasma insulin levels, $F(3.29, 78.96) = 45.8$, $P < 0.001$, $\eta_p^2 = 0.656$ (see Fig. 3).¹ We entered sex as a covariate to test whether there was a significant interaction. Whereas sex did not covary significantly with the increases in plasma glucose levels, $F(1, 24) = 1.1$, $P = 0.299$, it covaried with the increases in plasma insulin levels, $F(1,24) = 7.9$, $P = 0.010$. However, the interaction sex $\times$ time reflected that female participants had more durable increases in plasma insulin that did not differ

¹For one participant, the initial plasma insulin measure was missing. Thus, $n = 25$ for this analysis.

Figure 4.

Increased (red, food-control) and decreased (blue, control-food) activation for the food-cue reactivity contrast ($P < 0.001$, FDR corrected). Note that the numbers refer to the respective MNI coordinate of the slice. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

qualitatively. Thus, this covariate was not critical to our analysis because no significant differences between sexes were evident for the difference in plasma glucose and insulin right before and 25 min after the glucose administration, which is the best estimate for the increase during the second scan and will be used subsequently as an estimate of glucose and insulin reactivity.

Increases in blood plasma levels of glucose and insulin before and after administration of the OGTT were not correlated ($r = -0.04$, $P = 0.87$). Increases in insulin correlated significantly with mean subjective appetite ratings following food pictures ($r = -0.41$, $P = 0.038$) but not with mean subjective appetite ratings following control pictures ($r = -0.20$, $P = 0.318$). In contrast, increases in glucose correlated significantly with mean subjective appetite ratings following control pictures ($r = -0.41$, $P = 0.040$) but not with mean subjective appetite ratings following food pictures ($r = -0.21$, $P = 0.310$). Thus, insulin responses tended to be more strongly associated with cue-induced appetite ratings whereas glucose responses tended to be more strongly associated with ratings measuring primarily homeostatic hunger.

Imaging Results

Food-cue reactivity

To estimate the main effect of food-cue reactivity, we aggregated both runs. The presentation of food pictures compared to low-level control pictures strongly activated the dorsal and ventral stream (see Fig. 4). The most prominent bilateral network consisted of temporal (i.e., fusiform gyrus), limbic and paralimbic (i.e., thalamus, hippocampus, amygdala, cingulate cortex), striatal, insular, and orbito-in-

ferior frontal regions (Table I). This pattern corresponded very closely with the BOLD response covarying with subjective appetite (Supporting Information, Table S.I and Fig. S.2). There was bilaterally less activation to food versus control pictures in the superior parietal cortex, most notably in the inferior parietal lobule and the posterior precuneus.

Interaction of food-cue reactivity and homeostatic hunger

The administration of glucose led to reduced activation for food versus control pictures in the right basal ganglia (globus pallidus and caudate nucleus), the right medial frontal gyrus, the left middle temporal gyrus, and the left anterior cingulate cortex (see Table II and Fig. 5). In contrast, activation increased in the anterior precuneus and in occipital regions (i.e., cuneus, lingual gyrus).

To cross-validate reduced functional food-cue reactivity with behavioral ratings of subjective appetite, we extracted the mean signal change from the activated cluster in the right basal ganglia (i.e., the largest cluster with the highest local $t_{\max}$) using Matlab 7.1 (MathWorks, Sherborn, MA). Decreases in food-cue reactivity after the administration of glucose were positively correlated with decreases in subjective appetite ratings following control pictures ($r = 0.47$, $P = 0.016$) and tended to be significant for food pictures ($r = 0.35$, $P = 0.078$). Thus, reduced food-cue reactivity in the basal ganglia was associated with reduced subjective appetite, most notably after seeing control pictures which supports an association with homeostatic hunger.

Interaction of food-cue reactivity with insulin

High increases in blood plasma levels of insulin were associated with bilaterally reduced neural food-cue

TABLE I. Regions with significantly activated clusters showing food-cue reactivity, cluster size $k > 20$ and $t > 3.74$, $P < 0.001$ FDR corrected

Region	Side	k	MNI coordinates			$t_{\max}$
			x	y	z	
Food pictures-control pictures						
Fusiform gyrus	R	48072	28	-46	-18	21.27
Fusiform gyrus	L		-28	-54	-14	20.21
Inferior occipital gyrus	L		-46	-72	-10	18.78
Inferior temporal gyrus	L		-48	-74	-4	18.69
Parahippocampal gyrus	R		34	-32	-26	16.82
Middle occipital gyrus	R		42	-74	-14	15.44
Middle temporal gyrus	R		44	-78	10	15.25
Middle occipital gyrus	L		-30	-86	12	15.20
Inferior occipital gyrus	R		36	-74	-12	15.18
Cerebellum, hippocampus, thalamus, hypothalamus, putamen, caudate nucleus, globus pallidus, amygdala, insula, lingual gyrus, precuneus, superior parietal gyrus, inferior parietal lobule, inferior frontal gyrus	R, L					<15
Inferior frontal gyrus, middle frontal gyrus	R	2104	54	38	14	8.75
Cingulate cortex	R, L	314	4	2	30	7.56
Middle frontal gyrus, precentral gyrus	R	739	34	-8	48	5.87
Middle frontal gyrus, precentral gyrus	L	546	-34	-6	48	5.55
Postcentral gyrus	R	121	66	-14	26	5.29
Postcentral gyrus	R	167	56	-24	48	5.08
Cingulate cortex	L, R	124	-4	14	46	4.76
Control pictures-food pictures						
Inferior parietal lobule, supramarginal gyrus	R	250	62	-52	40	7.42
Precuneus	R, L	406	10	-58	36	6.80
Inferior parietal lobule, supramarginal gyrus, angular gyrus	L	124	-56	-56	46	6.06

reactivity in cerebellar, insular, striatal, cingular, inferior-frontal, prefrontal, and temporal regions as well as limbic regions (i.e., thalamus, amygdala, hippocampus) in the right hemisphere (Table III and Fig. 6). This pattern of

brain activation overlapped with the BOLD response associated with subjective appetite (i.e., in the fusiform gyrus, the prefrontal cortex, the precuneus, the postcentral gyrus, and in orbito-inferior-frontal, limbic, and paralimbic

TABLE II. Regions with significant change in food-cue reactivity after the administration of glucose, cluster size $k > 20$ and $t > 3.29$, $P < 0.001$ uncorrected

Region	Side	k	MNI coordinates			$t_{\max}$
			x	y	z	
Increase in food-cue reactivity						
Precuneus	R, L	784	2	−78	48	4.87
Cerebellum, lingual gyrus	L	416	−18	−84	−22	4.43
Cuneus	L	418	−2	−92	6	4.04
Fusiform gyrus	R	37	30	−60	−12	4.02
Posterior cingulate, cuneus	R	67	18	−68	6	3.93
Cuneus, middle occipital gyrus	R	69	16	−102	−2	3.92
Inferior/middle occipital gyrus, lingual gyrus	R	120	28	−86	−16	3.80
Decrease in food-cue reactivity						
Globus pallidus, caudate nucleus head	R	78	10	2	−4	5.11
Caudate nucleus body	R	46	26	−10	26	4.23
Middle temporal gyrus	L	26	−64	−22	−14	3.93
Anterior cingulate cortex	L	51	−8	22	18	3.91
Medial frontal gyrus	R	23	6	54	18	3.84

Figure 5.

(A) Increase (red) and decrease (blue) in activation after the administration of glucose for the contrast food pictures-control pictures (homeostatic hunger $\times$ food-cue reactivity, $P < 0.001$, uncorrected). Note that the numbers refer to the respective MNI coordinate of the slice. (B) BOLD signal change extracted

from the basal ganglia for the peak activation in the medial globus pallidus (MNI: $x = 10$, $y = 2$, $z = -4$). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

regions, Supporting Information Table S.II). This indicates that insulin is associated with the neural food-cue reactivity, scaling directly with subjective appetite (see Supporting Information).

Interaction of food-cue reactivity with glucose

The increases in blood plasma levels of glucose interacted negatively with the change in neural food-cue reactivity in the right hippocampus (see Supporting Information, Fig. S.1).

DISCUSSION

The design of our study allowed us to investigate simultaneously the complex interaction of cue-induced appetite and food-cue reactivity with homeostatic hunger and the increases of glucose and insulin blood plasma levels in response to an OGTT. To our knowledge, we are the first to investigate these regulatory responses to a standardized caloric intake in relation to the neural processing of food pictures. To summarize, we found that our design was effective to increase appetite through the presentation of pictures showing palatable food. In addition, it was effective in reducing appetite while increasing the blood plasma levels of glucose and insulin by the administration of glucose. As hypothesized, the association with subjective appetite ratings was echoed in the imaging data: A large bilateral network of temporal, insular, and orbito-

frontal regions, typically involved in processing of food stimuli, as well as limbic, paralimbic, and striatal regions, typically involved in homeostatic hunger, energy-dependent processing, and more generally reward [van der Laan et al., 2011], was strongly activated.

After the standardized caloric intake, neural food-cue reactivity decreased in the basal ganglia and paralimbic regions. Notably, those activated regions of the basal ganglia seem to be sensitive to leptin, a hormone that provides information about energy stores which is critical to body-weight regulation [Farooqi et al., 2007], and sensitive to overfeeding [Cornier et al., 2007]. Reported correlations with subjective appetite ratings support the relation to homeostatic hunger. The increase of activation to food versus control pictures in occipital and postero-medial regions after the glucose administration underlines one key element of the hedonic-hunger concept, which is dependency on the food environment [Lowe and Butryn, 2007]. Especially the anterior precuneus is involved in self-related, deliberate, and elaborate processing [Cavanna and Trimble, 2006]. This suggests that reduced appetite induces a more thorough and selective analysis of food opportunities, which may be echoed in the reduction of rating duration following control but not food pictures.

Fasting levels of glucose and insulin were not significantly correlated with food-cue reactivity. This is probably due to the fact that in healthy normal-weighted adults, the variance in fasting levels is low, especially compared to

TABLE III. Regions with change in food-cue reactivity significantly correlated with the increase in blood plasma insulin, cluster size $k > 20$ and $t > 3.29$, $P < 0.001$ uncorrected

Region	Side	k	MNI coordinates			$t_{\max}$
			x	y	z	
Negative interaction						
Cerebellum, parahippocampal gyrus	L	1545	-16	-46	-42	6.72
Precentral gyrus, middle frontal gyrus	L	379	-30	6	38	6.61
Superior temporal gyrus	L	1389	-64	-42	14	6.50
Thalamus, amygdala, insula, hippocampus, superior temporal gyrus	R	3277	20	-28	16	6.47
Cerebellum	R	2389	22	-34	-40	6.36
Precentral gyrus, paracentral lobule, precuneus	L, R	4842	-8	-26	80	6.32
Inferior occipital gyrus, lingual gyrus	R, L	370	22	-96	-14	5.94
Middle frontal gyrus	R	1275	28	24	26	5.48
Medial frontal gyrus, cingulate cortex	R, L	507	2	-12	50	5.01
Cingulate cortex, anterior cingulate cortex	L	320	-12	30	28	4.99
Cuneus, precuneus, superior parietal lobule	L	299	-20	-84	32	4.71
Fusiform gyrus	R	157	44	-48	-24	4.65
Caudate nucleus body	L	122	-20	16	8	4.65
Tuber, pyramis	L	358	-40	-70	-34	4.62
Middle temporal gyrus, posterior cingulate	R	174	42	-68	10	4.49
Posterior cingulate	L, R	159	-8	-44	18	4.49
Precuneus, cuneus	R, L	271	4	-76	48	4.49
Inferior/middle frontal gyrus	L	101	-36	30	6	4.47
Tuber	L	25	-50	-54	-36	4.44
Cingulate cortex	R	24	16	-44	36	4.39
Putamen	R	30	24	16	2	4.29
Precuneus, cuneus	R	143	14	-90	38	4.27
Precentral gyrus	L	29	-40	-12	64	4.25
Superior frontal gyrus	L, R	129	-4	14	54	4.11
Medial/inferior frontal gyrus	L	64	-14	34	-6	4.04
Caudate nucleus tail, parahippocampal gyrus	L	56	-22	-30	16	4.04
Middle frontal gyrus	L	26	-30	28	40	4.02
Angular gyrus	L	44	-40	-62	32	4.01
Insula	L	22	-42	0	12	3.98
Inferior frontal gyrus	R	29	54	38	16	3.95
Caudate nucleus head	R	80	6	8	2	3.94
Middle frontal gyrus	L	20	-36	44	30	3.90
Inferior occipital gyrus, fusiform gyrus	L	55	-14	-92	-14	3.81
Putamen	L	43	-28	-12	2	3.79

increases following the OGTT (see Fig. 3). Consequently, fasting levels of insulin were demonstrated to correlate with food-cue reactivity in a sample including participants with obesity [Wallner-Liebmann et al., 2010].

Increases in plasma insulin levels were associated with a decrease in neural food-cue reactivity in a widespread bilateral pattern of activation and the limbic system in the right hemisphere. Insulin was shown to affect activation in the fusiform gyrus in response to visual processing [Rotte et al., 2005]. In addition, we were able to replicate recent findings by Guthoff et al. [2010] who reported bilateral activation in the fusiform gyrus, the right hippocampus, the right superior temporal gyrus, and the right middle frontal gyrus (but with the latter two regions being bilaterally activated in our sample). They asked their fasting participants to discriminate food stimuli from nonfood stimuli and administered intranasal insulin using a placebo-con-

trolled design. This indicates that these regions are directly involved in food processing with higher insulin levels leading to less activation. Our results may further complement another recent study by Kullmann et al. [in press], who investigated lean and overweight participants using resting state functional connectivity measured by fMRI. They found that functional connectivity strengths in the left orbitofrontal cortex ($r^2_{\text{adjusted}} = 0.39$) of the prefrontal lobe network and the right putamen ($r^2_{\text{adjusted}} = 0.65$) of the basal ganglia network were negatively associated with an OGTT-derived insulin-sensitivity index (controlling for BMI and baseline insulin). Thus, both regions not only display insulin-dependently altered resting-state connectivity but also a reduction in activation related to food-cue reactivity that scales negatively with insulin increases. Given this convergence, it is tempting to hypothesize a common neural link that may provide a risk factor for developing

Figure 6.

Negative interaction with increases in insulin after the administration of glucose for the contrast food pictures–control pictures ($P < 0.001$, uncorrected). Scatter plots show the insulin increase plotted against the mean signal change extracted from anatomical masks of the fusiform gyrus, the orbitofrontal cortex, and the ventral striatum. Yellow circles indicate the clusters of activation inside those regions of interest that survived the threshold. Note that the numbers refer to the respective MNI coordinate. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

overweight and obesity [for further evidence regarding the striatal response, cf. Stice et al., 2008].

Notably, in our study insulin responses were related to subjective appetite. On the one hand, plasma level differences correlated significantly with cue-induced appetite ratings after glucose administration. On the other hand, the patterns of brain activity associated with plasma insulin reactivity and subjective appetite overlapped (i.e., in the fusiform gyrus, the postcentral gyrus, and in orbitofrontal, limbic, and paralimbic regions). Recently, the left lateral orbitofrontal cortex, and the postcentral gyrus and rolandic operculum were shown to be reliably associated with taste perception in a meta-analysis, thus providing a reasonable mechanism for insulin to alter the hedonic anticipation of taste [i.e., in our study insulin increases

were associated with decreasing food-cue reactivity in the ALE Clusters 3–5, as reported in Veldhuizen et al., in press].

Endogenous pancreatic insulin was hypothesized to regulate meal termination previously [cf., Vanderweele, 1994]. Consequently, manipulations of insulin levels were demonstrated to affect meal size and meal duration in rats [Surina-Baumgartner et al., 1995; Vanderweele, 1994]. However, additional insulin is not always effective [cf., Surina-Baumgartner et al., 1995]; especially in overnight-fasting humans, insulin infusions did not alter subsequent eating [Chapman et al., 1998; Woo et al., 1984]. It is important to note, though, that Chapman et al. [1998] demonstrated that an infusion of glucose, prepared to prompt similar plasma insulin levels as observed in direct insulin infusions, was subsequently accompanied by significantly reduced meal size. Similarly, Samra et al. [2007] found that food intake was reduced after consuming a glucose-containing drink, but more pronounced for the group of hyperinsulinemic men (i.e., fasting plasma insulin ≥ 41 pmol l^{-1}). Thus, results indicate that plasma insulin levels in response to an initial glucose intake may reduce caloric intake, possibly via devaluation of anticipated hedonic food-qualities, which would be echoed in delayed meal initiation after a preload or facilitated termination of a meal. This mechanism would explain the potential of high postprandial insulin secretion to predict lower rates of weight gain over a long-term period [Schwarz et al., 1995]. At first glance, this seems to contradict well-known findings of hyperinsulinemia in obesity [e.g., Modan et al., 1985]. However, reduced insulin sensitivity on a neural level may promote overeating leading to obesity [Tschritter et al., 2006; see also Schwarz et al., 1995] and hyperinsulinemia could be a compensatory response [for a canine model, see Bergman et al., 2007].

Limitations of the current study comprise that the OGTT led to the expected mean decrease in subjective appetite ratings but that decreases varied markedly between participants and not everyone experienced less appetite afterward. Thereby, our results rather apply to the dynamic postprandial interval where physiological satiation signals are still in flux induced by a standardized caloric intake. Second, we did not include a control group that received a noncaloric beverage instead of the OGTT to disentangle OGTT-related differences from repeated-measures effects and volume effects due to the mere ingestion of food. Though the decreased activation in the basal ganglia corresponded with decreased subjective appetite and crossvalidated the finding, including this control condition in a future study would be highly preferable because it will allow inferences independent of food ingestion. However, this is not likely to substantially bias the insulin and glucose effects. Third, though OGTT-derived indices of insulin sensitivity are common diagnostic measures for insulin reactivity, the reproducibility of OGTT results is usually mediocre so that a replication using more reliable tools (e.g., the euglycemic insulin clamp technique) is encouraged. Forth, though we outlined the advantages of the

OGTT that led to our decision, the OGTT provides less cephalic-phase stimulation [Teff, 2000] and less stomach distension than a nonliquid meal, which may lead to stronger and more diverse effects [cf., Inui et al., 2004]. Whereas this is a disadvantage in estimating the true effect sizes of food consumption, our results are less strongly influenced by these aspects and may reflect more clearly the caloric intake itself. Furthermore, we recorded no data on cerebral perfusion (e.g., by means of arterial spin labeling) to reliably estimate the association of plasma glucose and insulin levels on the control pictures before and after the administration of glucose. Given our behavioral results, we would expect insulin to primarily modulate hedonic aspects and glucose to primarily modulate homeostatic hunger. Using our data of neural response to food pictures, we were able to demonstrate the first but not the second because we measured only relative signal change, not absolute signal strength. In addition, changes in perfusion due to the OGTT may affect the magnitude of the BOLD response by physiological ceiling effects. Thus, a future study including cerebral perfusion measures may further substantiate these results and the proposed dissociation.

In conclusion, processing of food pictures activated a large bilateral network typically involved in homeostatic and hedonic aspects of hunger and this activation corresponded with ratings of subjective appetite. A standardized caloric intake reduced activation in striatal and paralimbic regions, most notably in the basal ganglia. Corresponding plasma insulin increases were associated with decreased neural food-cue reactivity in various bilateral regions (i.e., fusiform gyrus, insula, orbitofrontal cortex) and limbic regions in the right hemisphere. In particular, the insulin response modulated activation in regions also involved in cue-induced appetite and correlated with subjective ratings, most notably in the fusiform gyrus. In addition, plasma glucose increases were associated with decreased activation in the right limbic system as well. Our results suggest that glucose reactivity is primarily related to homeostatic regulation whereas insulin reactivity critically regulates the response toward food after caloric intake in healthy normal-weighted adults. This effect refers to an anticipatory response toward food, which is crucial for meal initiation and sensitive to caloric intake via consummatory behavior [Cornier et al., 2007], but future studies will need to explicitly address the effects of central insulin reactivity to consummatory behavior as well. By this mechanism, insulin responses may markedly retroact on behavior given our hedonically tempting food environment, eventually putting people with lower glucose-induced insulin responses at higher risk for hedonically motivated continuation of food intake.

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