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Food craving regulation in the brain: the role of weight status and associated personality aspects

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Food craving - the strong desire for particular food [1] - is a powerful trigger for food intake [2] and has been associated with obesity [1, 3] including dieting success [2]. Despite its relevance for successful weight control [1], current knowledge on weight-related differences in the underlying brain mechanisms is rather limited. Reasons for the lack of knowledge might be (1) the assumption of linear relationships between weight status and craving-related neural mechanisms or (2) the focus on normal-weight and obese samples with overweight individuals being underrepresented in previous studies [4–9]. Therefore, here we investigated neural correlates (BOLD activity and functional connectivity) of food craving regulation in a balanced sample of hungry normal-weight, overweight, and obese women; aiming at identifying relationships with weight status (focusing on quadratic associations) and obesity-relevant personality aspects. We first explored relationships between the *body mass index* (BMI), as a measure of the individual weight status, and general personality characteristics (i.e., sensitivity to reward/sensitivity to punishment [10] and impulsivity [11]) as well as eating-specific aspects of personality [12]. We found linear and quadratic relationships which were partly moderated by gender (publication 1). Relevant eating-specific aspects of personality (i.e., *Disinhibition* and *Cognitive Restraint*) were considered for the neuroimaging part of this thesis project. In this study participants were presented with pictures of palatable food and instructed to either admit to the upcoming craving or to regulate it. Regulation, in contrast to craving, was characterized by an inverted U-shaped association of BMI and brain activity in areas involved in food salience processing (putamen, amygdala, and insula), indicative of BMI-related variation in motivational signaling. Moreover, several differences in functional connectivity were observed. They suggest an increased need for top-down adjustment of striatal value representations with a higher BMI (linear relationship of BMI and connectivity of putamen/dorsolateral prefrontal cortex) and an impaired interplay between salience processing and self-monitoring or eating-related strategic action planning in highly disinhibited eaters (linear relationship of *Disinhibition* and connectivity of amygdala/dorsomedial prefrontal cortex or caudate) (publication 2). Although further research is needed to confirm the current findings, this thesis project contributes to a better understanding of the neural basis of food craving regulation in relation to weight status and differences in eating behavior. Identified regions may represent targets for real-time fMRI neurofeedback training paradigms for obesity treatment, an innovative approach that enables individuals to volitionally regulate brain activity of certain regions to induce changes in behavior [13–15].

List of Abbreviations

BAS	Behavioral Activation System
BIS	Behavioral Inhibition System
BIS-11	Barratt Impulsiveness Scale-11
BMI	Body mass index
BOLD	Blood oxygen level-dependent
CBF	Cerebral blood flow
CNS	Central nervous system
CR	Cognitive Restraint
DA	Dopamine
dACC	Dorsal anterior cingulate cortex
DIS	Disinhibition
dlPFC	Dorsolateral prefrontal cortex
dmPFC	Dorsomedial prefrontal cortex
fMRI	Functional magnetic resonance imaging
HUN	Susceptibility to hunger
lPFC	Lateral prefrontal cortex
NAc	Nucleus accumbens
OFC	Orbitofrontal cortex
PFC	Prefrontal cortex
PPI	Psychophysiological interaction
TFEQ	Three-Factor Eating Questionnaire
vmPFC	Ventromedial prefrontal cortex
VS	Ventral striatum
VTA	Ventral tegmental area

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1 Introduction

Obesity is a multifaceted phenomenon. A variety of interrelated factors contribute to overeating and the abnormal or excessive body fat accumulation characterizing overweight and obesity [17]. Such factors range from genetic aspects affecting body physiology and behavior [18, 19] to environmental characteristics including lifestyle or accessibility, price, and promotion of calorie dense food [20–23]. A mismatch between modern environment/lifestyle and biological processes which evolved in ancient times of food scarcity has been proposed to constitute the basis for the present obesity problem. Thus, biological traits such as strong attractability to high-caloric food, slow satiety mechanisms or high metabolic efficiency are advantageous in a scarce environment but detrimental in our modern societies with an abundance of food [24, 25]. Brain mechanisms involved in the processing of reward, learning and memory, for example, likely evolved to induce ingestion of palatable food beyond homeostatic needs to guarantee energy storage for times of food shortage or famine, having adverse consequences for health these days [26, 27].

To specify the degree of overweight or obesity and the associated risk for comorbidities, several classification systems are available. One commonly used measure to classify overweight and obesity in adults is the *body mass index* (BMI). The BMI is defined as an individual's weight in kilograms divided by the square of his or her height in meters (kg/m^2). The *World Health Organization* (WHO) defines six different weight categories [17]: (1) underweight (BMI < 18.50), (2) normal weight (BMI ≥ 18.50 $kg/m^2 < 25$ kg/m^2), (3) overweight (BMI ≥ 25 $kg/m^2 < 30$ kg/m^2), (4) obesity class I (BMI ≥ 30 $kg/m^2 < 35$ kg/m^2), (5) obesity class II (BMI ≥ 35 $kg/m^2 < 40$ kg/m^2), and obesity class III (BMI ≥ 40 kg/m^2). Above a BMI of 25 the risk of comorbidities, such as cardiovascular diseases, continuously increases with BMI [17]. Although the BMI provides the most useful population-level measure of overweight and obesity, it does not account for differences in body fat distribution and may not correspond to the same degree of fatness in different individuals [17]. However, obese individuals with abnormal intra-abdominal fat depots are at particular risk of the adverse health consequences of obesity [28]. Measurement of waist circumference, therefore, provides a convenient and simple method of identifying individuals at increased risk of obesity-associated diseases due to abdominal fat distribution. A waist circumference of ≥ 102 cm in men and ≥ 88 cm in women is categorized as abdominal obesity [17]. Another approach to classify obesity is the *Edmonton Staging System* that proposes four stages of obesity (in addition to a stage 0 without any indication for obesity). Classification is based on the evaluation of obesity-related comorbidities, physical and psychological symptoms, as well as potential impairments in quality of life [29]. The staging system aims at complementing existing anthropometric systems by providing indication of obesity-associated disease extent and severity [29].

Worldwide obesity is on the rise (Fig. 1). The prevalence nearly doubled between 1980 and 2008, especially in higher income level countries [30]. According to the WHO, an alarming prevalence is being reached in America with 62% of the population being classified as overweight[1] and 26% as obese[2]. These individuals are at a higher risk for coronary heart disease, ischemic stroke, type 2 diabetes, and several cancer diseases [30]. Every year around 3 million people die because of overweight or obesity [30].

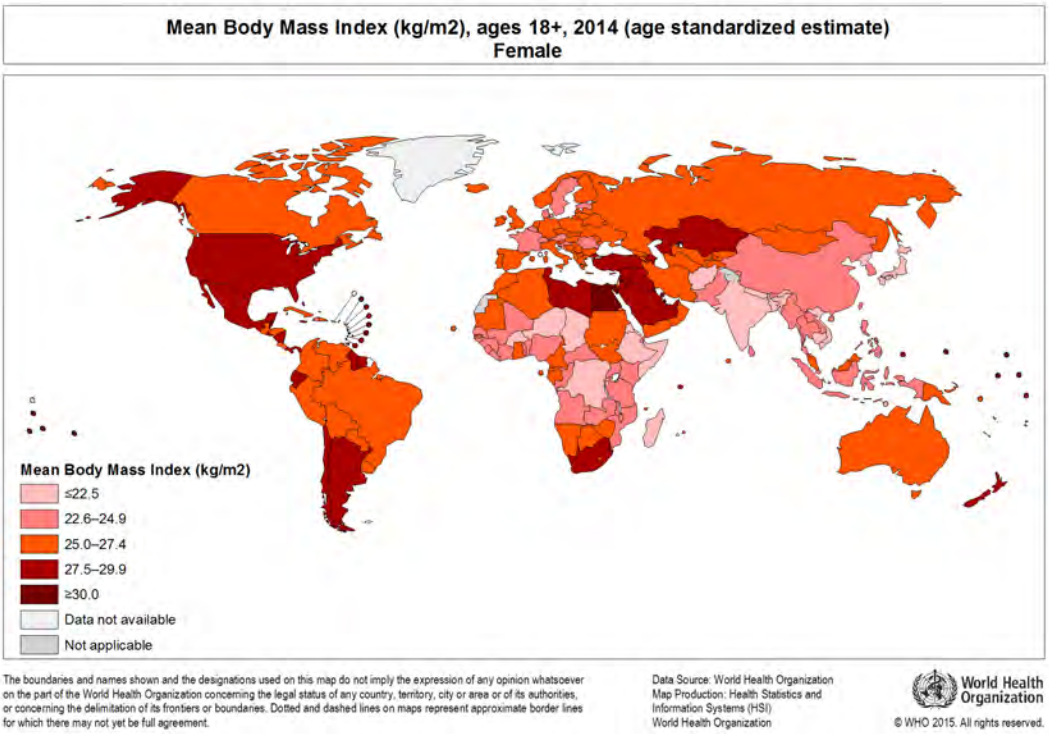

Figure 1: Situation of worldwide obesity (2014, females). Reprinted with permission from the WHO.

Considering the rising prevalence levels of obesity and associated health risks, rigorous intervention approaches are needed to prevent and treat this health problem. Unfortunately, standard lifestyle interventions show just small and short-lived changes in BMI ($\sim 5\%$) [31–37], as dieters typically find it difficult to stop unhealthy eating habits [38]. So far, bariatric surgery is considered the most effective method for large and long-term weight loss [39–42], resulting in a substantial improvement of cardiovascular risk factors and quality of life [43–45]. Therefore, it is the therapy of choice for patients with severe obesity. However, it is an invasive intervention with several side effects [46–48]. For instance, patients have to compensate nutritional deficits by daily multivitamin and mineral supplements [46, 49, 50]. After the surgery patients may also suffer from depressive symptoms increasing suicide rate [51]. To establish more effective non-surgical interventions, we

[1] BMI ≥ 25 kg/m^2 < 30 kg/m^2
[2] BMI ≥ 30 kg/m^2

have to learn more about the underlying mechanisms that lead to and maintain unhealthy eating behavior. Therefore, this thesis project is dedicated to one of these processes - food craving. Food craving is defined as the inner drive or desire to eat certain foods [1]. According to its relevance for overeating and obesity [1], the present thesis project focuses on the examination of brain regulation of food craving and its relationship with weight status and associated psychological traits. Specifically, the following research questions will be addressed: (a) Which aspects of personality are relevant for obesity and thereby interesting for the study of food craving regulation?, and (b) How are weight status or obesity-associated psychological traits linked to brain regulation of food craving? Insights may be used to develop novel intervention modules, such as neurofeedback training, or to design personalized treatments based on the patient's personality structure.

In the following two sections, I will introduce mechanisms involved in the homeostatic (section 1.1) and hedonic (section 1.2) regulation of eating, including obesity-related alterations in these systems. The focus will be on hedonic (i.e., reward) eating. Specifically, current knowledge on functional imaging of the brain network for appetite, including literature on food craving and its regulation, will be presented. Section 1.3 will be dedicated to the introduction of current knowledge on associations between psychological traits and obesity. Based on the summarized literature, I will derive the rationale for the experimental work in section 1.4. This experimental work resulted in two publications that form the present cumulative dissertation (chapter 2). I close with a summary of the thesis project (chapter 3).

1.1 Homeostatic eating

According to the process of energy homeostasis, human body weight and body fat content are relatively stable over time [52]. The energy homeostasis system matches energy intake to energy expenditure over long time periods. Circulating signals (nutrients and peptides from the periphery) inform the brain (e.g., hypothalamus) of available energy stores. In response, the brain adjusts food intake by signaling hunger or satiety which then affects energy intake and energy expenditure [53, 54].

1.1.1 Neurocircuits involved in the homeostatic regulation of eating

The central nervous system (CNS) regulates energy intake and expenditure by integrating *anorexigenic* or appetite inhibiting (e.g., leptin, insulin, peptide YY [PYY], glucagon-like peptide [GLP-1], cholecystokinin [CCK], melanocortins, oxytocin) and *orexigenic* or appetite stimulating (e.g., ghrelin, agouti-related protein [AGRP], neuropeptide Y [NPY], γ-aminobutyric acid [GABA]) signals [55]. Peripheral anorexigenic input into the CNS can be divided into long-term signals circulating in proportion to body fat stores (e.g., the hormones leptin and insulin [56–60]) and short-term meal-related signals from the gut (e.g., peptides such as CCK, GLP-1, and PYY [61–63]). Also meal-related nutrient sensing contributes to this short-term input [64]. The stomach-derived hormone ghrelin provides peripheral orexigenic input into the CNS [65]. Figure 2 summarizes the main signals involved in homeostatic eating regulation.

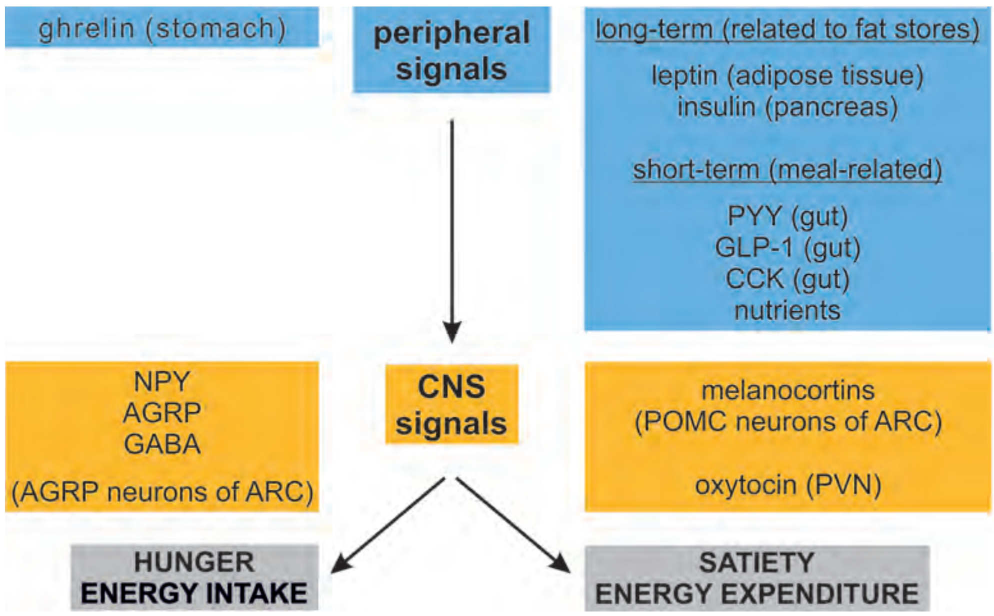

Figure 2: Main signals involved in the homeostatic regulation of eating (respective sites of release in brackets). The central nervous system (CNS), especially hypothalamus, senses peripheral hunger (ghrelin; left) and satiety (leptin, insulin, PYY, GLP-1, CCK, nutrients; right) signals. In response to the peripheral stimulation, neurons in the hypothalamic arcuate nucleus release neuropeptides and neurotransmitters into downstream neurons (e.g., PVN releasing oxytocin) to initiate hunger/energy intake (NPY, AGRP, GABA) or satiety/energy expenditure (melanocortins). Abbreviations: AGRP agouti-related protein, ARC arcuate nucleus, CCK cholecystokinin, GABA γ-aminobutyric acid, GLP-1 glucagon-like peptide, NPY neuropeptide Y, POMC pro-opiomelanocortin neurons, PVN paraventricular nucleus, PYY peptide YY.

Signaling of the hormone leptin provokes satiety [66, 67] by enhancing the responsiveness to gut-derived anorexigenic signals [68, 69] of neurons located in the forebrain (e.g., arcuate nucleus of the hypothalamus [ARC]) [70] and hindbrain (e.g., nucleus of the solitary tract) [71]. However, hypothalamic ARC neurons also contribute to hunger and energy intake [72]. While leptin inhibits agouti-related protein (AGRP) neurons in the ARC - resulting in satiety, these neurons are activated by the stomach-derived hormone ghrelin - provoking hunger [73]. Ghrelin-binding induces the release of several orexigenic neuropeptides (e.g., NPY or AGRP) and neurotransmitters (e.g., GABA) into downstream neurons of, for example, those in the hypothalamic paraventricular nucleus (PVN), stimulating feeding. Other ARC neurons - pro-opiomelanocortin neurons (POMC) [74, 75] - inhibit food intake through leptin stimulation and the release of the anorexigenic α-melanocyte stimulating hormone (α-MSH) after binding to melanocortin receptor 4 (MC4R) in the PVN [73, 76, 77]. AGRP can inhibit these POMC neurons. Strikingly, leptin, insulin and ghrelin also affect dopaminergic signaling thereby influencing motivational processes of food intake [78, 79].

1.1.2 Homeostatic eating and obesity

The above described processes ensure that the body 'defends' itself against weight loss and weight gain in normal-weight individuals [80–83]. Sufficient availability of energy stores or nutrients and corresponding neural signaling restricts further enhancement. Decreasing neuronal input from these peripheral signals stimulates the brain to signal deficiency of stored energy and available nutrients to raise energy stores and nutrient levels. Remarkably, overweight and obese individuals 'defend' their body fat stores - although increased - as well [84–86]. Potential causes are impairments in the secretion of insulin or leptin; dysfunction in hypothalamic sensing of adiposity-, meal-, or nutrient-related signals; or alterations in the neuronal sensitivity to these inputs [87]. A frequently discussed explanation, for instance, is leptin resistance [55]. Leptin levels are typically increased in obese animals and humans, but its function to reduce food consumption is blunted in obesity. Although the cause of leptin resistance is still unknown, diet-induced inflammation, gliosis or injury [88–92] affecting hypothalamic cells supposedly play a role, leading to impaired responding to leptin. As a consequence, for 'normal' energy homeostasis leptin needs to be increased leading to an expansion of body fat stores to adapt leptin levels until a new steady state is reached and stabilized. Similar to leptin, diet-induced inflammatory processes are supposed to blunt the anorectic effect of insulin, promoting hyperphagia and weight gain [91, 93]. According to such adverse processes weight loss interventions in obesity might be counteracted by homeostatic mechanisms [94, 95].

1.2 Hedonic eating

The mere sight of palatable food can trigger food consumption just for pleasure and beyond homeostatic needs. It has been speculated that such reward-related aspects of eating evolved to motivate engagement in food consumption in order to store energy for times of scarcity [96]. Reward-related eating might be subdivided into three phases. In the preparatory phase food reward is anticipated. This phase is crucial for decision making, i.e., whether or not to approach and consume available food. To anticipate the rewarding properties of attractive food the brain uses representations of reward expectations and effort/risk requirements from prior experiences to optimize choices [97–101]. The preparatory period is followed by the consummatory phase. In this stage initial reward expectancy is confirmed or rejected. During food consumption pleasure is directly derived from gustatory and olfactory sensations which drive consumption until satiation signals dominate. After meal termination the postconsummatory phase starts and last until the next meal. As nutrient sensing in, for example, the gastrointestinal tract supposedly also contributes to the generation of food reward, this stage adds to the reinforcing power of food [102].

A food reward consists of two components: pleasure (*liking*) and motivation (*wanting*). The affective part or food *liking* is associated with the hedonic reaction to the pleasure of a food reward, whereas the motivational part or *wanting* relates to incentive salience [103–105]. Incentive salience is generally triggered by rewards and their predictive cues - previously neutral stimuli which acquired reward properties after being repeatedly linked to, e.g., the consumption of palatable food [106] [107–109]. It makes these cues or associated actions attractive and desirable. Although *wanting* and *liking* typically go together, excessive incentive salience may in some cases lead to irrational 'wants' for outcomes that are not pleasurable or *liked* [110, 111], as proposed for compulsive drug taking in substance addiction and aspects of overeating in obesity [112, 113]. Physiological states such as hunger or satiety directly modulate incentive salience assigned to food rewards [114]. Whereas hunger elevates the incentive salience of food rewards and their cues [114, 115], satiety is supposed to dampen food attractability [114]. Besides their effects on the motivational aspect of reward, physiological states also modulate food pleasantness [114, 116–118]. The components of food reward, moreover, are closely related to the concept of craving [119]. Craving describes the intense desire for a particular substance, such as food [1, 120]. Food craving is a strong motivational state, closely related to hunger [121] - although more intense and specific [122]. Cravings are considered to be an important component of addiction [123], predicting treatment outcomes for substance addictions [124, 125]. Food cravings have been positively linked to BMI [3, 126, 127] and the consumption of sweets or high-fat food [126]. Changes in craving might discriminate between successful and unsuccessful dieters, with a reduction of craving resulting in weight loss [2, 128].

1.2.1 Neurocircuits involved in hedonic eating

Pleasant foods have been shown to activate cortical regions like the orbitofrontal cortex (OFC), anterior cingulate cortex (ACC), and insular cortex in addition to subcortical forebrain structures such as the ventral striatum (VS), ventral pallidum, or amygdala; as well as mesolimbic dopaminergic projections and deep brainstem areas [104, 107, 129–135]. Neuroimaging studies in humans suggest that the subjective pleasantness of food, as measured by subjective ratings, is particularly coded within portions of the OFC [110, 131].

In animals, only subconscious components of pleasure and aversion are experimentally available, measuring positive and negative orofacial expressions when tasting respective stimuli [136]. Such studies indicate the presence of opioid mediated *liking* hotspots in the medial shell subdivision of the Nucleus accumbens (NAc, part of the VS) and the ventral pallidum [114, 137–144]. Similarly, opioids stimulate food *wanting* in a large zone throughout the entire NAc and other brain structures including amygdala and neostriatum in animals [145–148]. However, the most important *wanting* component, purely modulating motivational processes, seems to be dopaminergic signaling within the mesolimbic dopamine (DA) projection system [103, 109, 149, 150]. These projections arise from neurons in the midbrain ventral tegmental area (VTA) and project to the NAc in the ventral striatum [151]. Depending on their pleasantness, attractive foods (and other rewards) or associated cues trigger mesolimbic DA release [116, 151–154]. Phasic activity of dopaminergic projections from the VTA to the NAc is particularly involved in the decision making process during the preparatory phase of hedonic eating behavior [101, 102], potentially affecting food craving. Nevertheless, DA signaling in the NAc also appears to play a role in the consummatory phase, as DA levels and turnover continue to increase when food is consumed [155–157]. In addition to that, DA mediates food-related reward effects that are driven by energy content, as has been indicated by calorie-dependent DA changes in NAc that were unrelated to taste [158–161].

Functional imaging of the desire for food In recent years, the development of neuroimaging modalities, such as magnetic resonance imaging (MRI) or positron emission tomography (PET), has allowed the examination of brain anatomy and brain activity. Functional magnetic resonance imaging (fMRI) provides an indirect measurement of neuronal activity. It is based on neurovascular coupling, i.e., the assumption that synaptic neuronal activity is associated with a proportionate increase in local cerebral blood flow (CBF) [162, 163]. Functional MRI measures changes in CBF using the the so-called blood oxygen level-dependent (BOLD) signal [164]. This signal is sensitive to changes in blood oxygenation and corresponding local magnetic field inhomogenities [165–167], induced by neural activity while performing an experimental task in the MRI scanner. The resulting fMRI dataset of a participant is typically analyzed using the general linear model (GLM) approach [168]. In its simplest formulation the GLM can be expressed as: $Y = X\beta + \epsilon$ (1). Y represents the BOLD signal associated with a single voxel (3-D element). X is the design matrix describing the experimental paradigm. β represents the unknown weights setting the magnitude and direction of the association between the paradigm X and the data Y. The vector ϵ contains error values. β estimates of certain experimental conditions can be contrasted against each other to assess the relative difference between, e.g., *food pictures* vs. *control items*. The resulting images are thresholded statistical maps. They map brain areas showing significantly stronger CBF response. The contrast *food*

pictures vs. *control items* thus may map areas which represent the incentive salience of the presented food cues. As signal changes from brain activation are rather small, data from several participants have to be combined. For this combination individual brain images are transformed into a standard coordinate space [169], allowing the application of statistical tests to each voxel of the combined images [170].
As food selection is heavily guided by the visual system, typically visual food cues are used in corresponding neuroimaging studies. The sight of food is thought to elicit a wide range of anticipatory responses that likely determine our feeling of appetite for attractive food and associated eating behavior [171]. Visual food stimulation triggers emotional responses like the desire to eat [172], a main component of eating initiation. It also activates cognitive processes such as memory retrieval and hedonic evaluation based on previous experiences with the food [26, 173]. Additionally, self-control processes (e.g., dietary restraint) may be triggered [174, 175]. Several variables such as homeostatic state, stress, self-control, personality and eating style may influence the BOLD signal in food-related tasks [16].

The appetitive network On the basis of previous human neuroimaging studies, the appetitive network has been recently characterized [16]. It integrates homeostatic information on energy stores with external or internal food sensations and higher-order cognitive information on dietary goals (Fig. 3). Four interconnected brain areas form the core of this network: amygdala including hippocampus, OFC and adjacent vmPFC, striatum, and insula. These regions respond to food cues [16]. Activity depends on personality characteristics (e.g., [176, 177]) and can be modulated by homeostatic signals from the hypothalamus or the periphery [54, 55, 178]. Dopaminergic neurons, mainly originating in the midbrain (VTA and substantia nigra pars compacta [Snc]) [53], innervate these brain structures. This dopaminergic neurotransmission plays two roles: it acts as a learning and as a motivational signal [16]. Following food ingestion, DA provides a measure of the nutritional (i.e., reward) value of the consumed foods, thereby acting as a learning signal [152, 179]. After learning consolidation, though, DA is released in response to external food cues (e.g., sight) as an anticipatory reward signal which motivates approach and consumption of rewarding foods. Considering the core regions' specific functions, amygdala and OFC code the incentive value of food cues [180]. The amygdala is considered to assign value to sensory stimuli and to pass that information to the OFC/vmPFC. Here, the current absolute subjective value is computed [181, 182] and used for decision making. Importantly, the amygdala encodes stimulus salience, i.e., both positive and negative valence of a stimulus [183, 184] and is sensitive to contextual information to adjust the motivational level. The anterior insula, including adjacent frontal operculum, encodes multimodal sensory features of food [185]. This area constitutes the primary taste cortex [186], but also receives somatosensory projections from the oral cavity [187] as well as visceral afferents from the gut [188]. However, the sight of food is sufficient enough to activate the insula; thus, it might be involved in higher-order processing of food [185]. Posterior and mid-insula portions are particularly responsible for the integration of interoceptive signals and interoceptive awareness [189]. The striatum, which is the main projection site of DA neurons, is significantly involved in motivated behaviors and incentive learning. Striatal signaling helps to transform value signals into action plans. This area is strongly responsive to conditioned cues which motivate individuals to approach and consume food by creating incentive states [103]. The core regions of the appetitive network are under cognitive control, mainly exerted by the ACC and lPFC which work in concert to evaluate and compare options to channel behavior [190, 191]. Depending on context and goals, these regions either enhance appetite and motivation to eat or suppress it. Signaling in these areas, therefore, does not automatically implicate self-control. The dorsal ACC plays a crucial role in error awareness and conflict monitoring [192, 193]. The lPFC, on the other hand, is involved in planning of behavior to achieve goals but also in encoding of reward values [194]. For adaptive behavior, the dorsolateral prefrontal cortex (dlPFC) incorporates contextual information with external input and internal signals such as hunger [195].

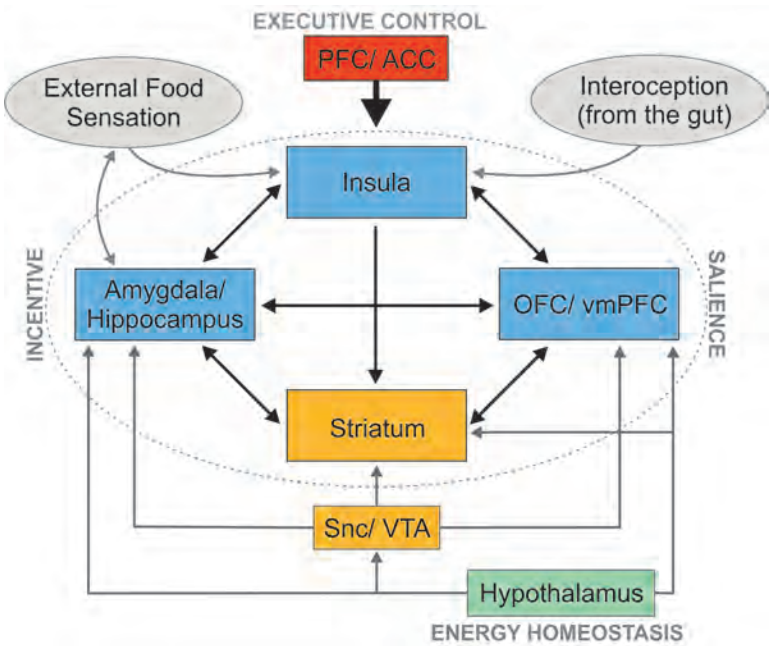

Figure 3: The appetitive network. Core regions (within dashed circle) respond to external food cues to create incentive states and motivate food approach/consumption. The core regions are modulated by homeostatic signals from the hypothalamus, direct peripheral input or interoceptive signals from the gut. Higher-order executive control signals from the PFC/ACC either enhance or reduce the appetitive response (adapted from [16]). Abbreviations: ACC anterior cingulate cortex, PFC prefrontal cortex, Snc substantia nigra pars compacta, vmPFC ventromedial prefrontal cortex, VTA ventral tegmental area.

Regulation of the desire for food: insights from functional neuroimaging One of the major drivers of overeating is food craving [1]. Enhanced BOLD activity within reward-sensitive regions of the appetitive network (VTA, VS, insula, operculum, OFC/vmPFC) has been observed during instructed food craving [196]. Cognitive regulation (e.g., reappraisal or mental distancing) of food craving, on the other hand, induced a decrease in reward-related activity [7, 197, 198] in contrast to increased activity in areas associated with top-down control (lPFC, dACC) [4–7, 197]. Strikingly, relationships between weight status and neural correlates of craving regulation are still an open issue. Previous findings are inconsistent: some studies report decreased activity in top-down executive control areas (lPFC, dACC) [6, 7], others did not find such associations [4, 5].

1.2.2 Hedonic eating and obesity

Evidence is accumulating that obesity is associated with impairments in brain structures associated with reward processing [102]. Obesity, in contrast to normal weight, has been related to elevated cue-induced incentive salience and value processing (e.g., insula, OFC, amygdala, striatum), alterations in emotion processing and memory retrieval (e.g., insula, amygdala, cingulate gyrus, striatum, hippocampus), dysregulation of decision making networks (OFC, PFC, thalamus) and altered visual processing (e.g., thalamus, fusiform gyrus) [199–202]. Decreased activity of executive control regions in response to the presentation of cues signaling palatable food supposedly further affect reward processing in obesity [203]. These findings are indicative of dysregulation within the appetitive network in obesity, i.e., greater attribution of incentive salience to food cues supposedly driving overeating [16, 199, 201, 204–207]. Further, reactivity of the appetitive network appears to inappropriately adapt to satiety, as obesity is linked to increased activity in areas involved in decision making (PFC, OFC, caudate), reward anticipation (anterior cingulate, OFC), and emotional processing (insula, caudate, amygdala) in the sated state [202, 208, 209].
Besides alterations in reward anticipation, brain responding linked to food consumption might be also impaired in obesity. Neuroimaging studies indicate both hypo- [161, 207, 210–213] as well as hypersensitivity to food reward delivery in obesity [214]. According to the *reward deficiency hypothesis*, obese individuals overeat to compensate a diminished experience of subjective reward from food intake [161, 212, 213, 215]. This has been suggested to be caused by reduced dopaminergic D2/D3 receptor availability [113, 216, 217]. In contrast to that, hypersensitivity to food reward has been indicated by enhanced reactivity of the reward system in adolescents gaining weight, suggested to increase the risk for overeating and obesity [207]. Merging both concepts, Horstmann et al. (2015) proposed a non-linear relationship between human obesity and dopaminergic signaling [113]. According to this model, overweight and mild obesity might be paralleled by a low DA tone and exaggerated phasic DA responding in the striatum, resulting in high sensitivity

to reward. Severe obesity, on the other hand, may be accompanied by an increased DA tone and blunted phasic striatal DA firing, resulting in a reward deficit [113].

1.2.3 Interactions between the hedonic and homeostatic eating systems

Homeostatic status and food reward strongly influence each other. In circumstances of food deprivation, food reward and the motivation to seek out food is enhanced, whereas food becomes less rewarding and motivationally salient in times of repletion [55]. Key metabolic and hormonal signals regulating homeostasis co-modulate reward-related circuitry and operate by direct and indirect effects on DA function [55]. For example, the anorexigenic hormones insulin and leptin do not only affect energy homeostasis but also reduce DA release, facilitate its synaptic reuptake, and can decrease DA neuronal excitability [78, 218]; whereas the 'hunger-hormone' ghrelin enhances DA function. These hormones either directly modulate DA neurons in the mesolimbic circuitry or indirectly influence DA function via the lateral hypothalamic area (LHA) which integrates reward-related input (e.g., from NAc) with information about energy homeostasis from the ARC nucleus. In turn, LHA orexin neurons (amongst others) project to and modulate mesolimbic DA structures as well as hindbrain areas [79, 219]. Importantly, the neural loop including LHA, NAc, and VTA is necessary to attribute incentive salience to goal objects by making metabolic state signals available to the LHA [79, 101, 106, 220, 221]. Conversely, purely hedonic cues (such as the smell or sight of food) can, for example, trigger ghrelin release from the stomach [222].

1.3 Personality traits and obesity

Although many people have difficulties resisting food temptations, ultimately resulting in overweight and obesity, others manage to withstand and maintain a healthy weight. Personality differences seem to play a role in this phenomenon. Certain personality characteristics appear to predispose to weight gain whereas others may help to maintain a healthy body weight.

1.3.1 Neurocognitive tasks and obesity

Obesity has been frequently associated with general or specific personality characteristics measured by neurocognitive tasks [223]. These tasks cover domains ranging from executive function to time judgment, attention, visuospatial and language abilities, motor control, memory, and food motivation [223]. Vainik et al. [223] showed in a recent review that maladaptive eating behavior and high BMI were most consistently related to lower performance in executive function and enhanced food motivation. More specifically, the most sensitive measures of executive function captured the subdomains response inhibition (especially *Stroop test* [224–227] and *stop signal task* [228–230]), working memory (particularly *Austin maze task* [225]) and, although to a lesser degree, decision making (especially *delay discounting* [231–234]) [223]. The interaction of low executive function in combination with high food motivation (best measured by the *relative value of food task* [235–237]) was more strongly associated with maladaptive eating behaviors or BMI than these measures alone [223, 229, 231, 238–240].

1.3.2 Personality questionnaires and obesity

Another approach relates aspects of obesity to general or eating-related personality scales [223]. Large-scale studies showed that the general personality domains of the Five-Factor Model of personality [241, 242] are related to obesity [223]. The Five-Factor Model is a widely used approach to categorize personality based on five broad domains: *Neuroticism, Extraversion, Openness/Intellect, Agreeableness* and *Conscientiousness* [241, 242]. *Neuroticism* is a measure of the sensitivity to punishment and negative affect. *Extraversion* characterizes the sensitivity to reward and positive affect. *Openness/Intellect* measures cognitive and perceptual flexibility and exploration. *Agreeableness* measures altruism as opposed to exploitation of others. *Conscientiousness* represents a measure of top-down control over impulses that facilitates goal-directed behavior [241, 242]. These domains can be divided into several intercorrelated subdomains. For example, *Neuroticism* includes the subdomains N1: *Anxiety*, N2: *Angry Hostility*, N3: *Depression*, N4: *Self-Consciousness*, N5: *Impulsiveness*, and N6: *Vulnerability*. Individuals with obesity tend to score higher in aspects of *Neuroticism* and lower on aspects of *Conscientiousness*, show aspects of high *Extraversion* and low *Agreeableness* [243–245]. A more precise characterization via subdomains of these scales showed that obese individuals tend to be less stable and able to resist temptations (high level of N5: *Impulsiveness*), are assertive/wanting (high level of E3: *Assertiveness*, low level of E4: *Activity*) and show diminished scores on self-control (low level of C2: *Order*, low levels of E4: *Self-Discipline*) [244, 245]. The most crucial subdomain seems to be *Impulsiveness* (N5). Impulsivity - a multidimensional construct - might be generally described as the tendency to act without adequate forethought, including aspects such as responding rashly and without reflection, poor response inhibition, or preference of smaller immediate rewards instead of larger delayed ones [246]. Although it has been mainly related to BMI via the broad personality scales, impulsivity-specific questionnaires correlate with aspects of obesity as well [228, 247–252]. Additionally, the related psychological concept of self-control has been associated with weight gain and eating behaviors [253]. Another obesity-relevant model of personality is grounded in reinforcement sensitivity theory [254–257]. Based on this theory, two motivational systems underlie behavior and affect: the behavioral activation system (BAS) and the behavioral inhibition system (BIS), which can be assessed by the *BIS/BAS Scales* [10]. The BIS is the aversive motivational system which drives behavioral inhibition. It is characterized by sensitivity to punishment and negative affect. The BAS represents the appetitive motivational system which drives behavioral approach. This system is sensitive to reward and positive affect. Sensitivity to reward has been previously related to obesity [258–262]. The relationship with BMI seems to be curvilinear (inverted U-shaped), with less sensitivity to reward in normal weight and morbid obesity compared to overweight and mild obesity [258]. Sensitivity to punishment might be enhanced in obesity, indicated by heightened *Neuroticism* [243–245]. Sensitivity to punishment has also been related to eating disorders (Harrison 2010, 2011). For instance, there is the observation of a positive relationship between symptoms of binge eating and sensitivity to punishment (Davis 2013). Strikingly, studies on relationships between self-report measures of reinforcement sensitivity and obesity or eating disorders are mainly restricted to females, with males being underrepresented.

1.3.3 Eating-specific personality questionnaires and obesity

Several decades of research differentiated at least five eating-related personality constructs: *Cognitive Restraint* (extent of conscious efforts to restrict food intake to achieve long-term weight goals), *Disinhibition* (overeating tendencies provoked by emotional or situational triggers), *Susceptibility to Hunger* (extent to which hunger feelings are experienced and evoke food intake), *Emotional Eating* (overeating in response to emotional distress), and *External Eating* (overeating in response to external food cues) [12, 263]. These constructs have been frequently related to overweight and food intake [264–267]. For example, *Disinhibition* is robustly positively related to BMI [264, 268–270]. However, the relationship between *Cognitive Restraint* and BMI is less straightforward, indicating a curvilinear relationship, as negative and positive relationships with characteristics of obesity and weight management have been reported [265]. Strikingly, these eating-related personality traits are not independent from each other but interact instead [12, 271–274].

1.3.4 Underlying brain mechanisms of personality questionnaires in the food context

Little is known about relationships between personality characteristics and the underlying food-related brain mechanisms. Modulating effects of *Cognitive Restraint* [5, 275–279] as well as *Disinhibition* [199, 280] on the neural responses to food cues have been reported. Individuals scoring high on *Cognitive Restraint* [5, 277, 278], interested in their diet [281], or focusing on health aspects of food [282] showed stronger activation in executive control and attention areas such as the lPFC and lateral OFC in response to viewing food pictures. Higher scores of *Disinhibition* were related to increased activation in the vmPFC and decreased ACC response to visual food cues [199, 280]. Another study showed that differences in the sensitivity to external food cues interacted with the reward network's response to appetizing food pictures. More specifically, *External Eating* scores modulated functional connectivity between ventral striatum, amygdala, ACC and premotor cortex while viewing appetizing compared to bland foods [177]. Further, a high level of *Emotional Eating* has been associated with strong dopaminergic striatal responses to gustatory and olfactory stimuli [283] as well as greater activity in parahippocampal gyrus, ventral pallidum, thalamus and ACC during the anticipation and/or consumption of palatable food (i.e., milkshake) [284]. Besides these food-specific measures, sensitivity to reward, as measured by the *Behavioral Activation Scale (BAS)* [10] has also been shown to modulate cue-induced neural responses in reward-related regions in the frontal cortex, striatum, amygdala and midbrain [176]. A recent meta-analysis, which summarized the current knowledge on personality characteristics in relation to food-induced brain activation revealed high variability in the results within single personality characteristics and interrelated constructs [285]. According to this low concurrence, core neural correlates of personality aspects in the food context are still to be identified.

1.4 Rationale of the experimental work

From the current state of knowledge, as summarized above, we derived the necessity for the following experimental work:
From the current state of knowledge, we derived the need for (a) an in-depth characterization of the relationships between aspects of personality and human weight status, and to (b) examine the link between weight status or associated personality aspects and brain mechanisms of food craving regulation. Consequently, the aims of the present thesis project are two-fold:

Study 1) To establish a regression model for BMI including the most obesity-relevant general and eating-specific personality traits, including testing for linear and non-linear relationships.

Study 2) To examine the relationships between brain mechanisms of food craving regulation (i.e., BOLD activity and functional connectivity as measured by fMRI) and weight status or the afore characterized personality traits (focusing on the eating-specific aspects *Cognitive Restraint* and *Disinhibition* [12]) in a balanced sample of normal-weight, overweight and obese females.

We hypothesized *Cognitive Restraint*, *Disinhibition*, *Susceptibility to Hunger* (*Three-Factor Eating Questionnaire [TFEQ]*) [12] as well as sensitivity to reward/sensitivity to punishment (*Behavioral Inhibition System/Behavioral Activation System [BIS/BAS] Scales*) [10] and impulsivity (*Barratt Impulsiveness Scale [BIS-11]*) [11] to collectively explain variance in body weight status (i.e., BMI). We further expected to observe a non-linear (inverted U-shaped) relationship of *Cognitive Restraint* [12] and BMI, with the relationship being moderated by the level of *Disinhibition* [12].

With respect to brain regulation of food craving, we expected to observe quadratic relationships between BOLD activity and functional connectivity and BMI in areas involved in executive control and motivational processing. In addition to weight status, we hypothesized *Cognitive Restraint* to be related to the responding of executive control regions and *Disinhibition* to scale with reward and motivation related brain responding.

2 Experimental work

2.1 Publication 1: Dietrich et al., 2014

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Body weight status, eating behavior, sensitivity to reward/punishment, and gender: relationships and interdependencies

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Behavioral and personality characteristics are factors that may jointly regulate body weight. This study explored the relationship between body mass index (BMI) and self-reported behavioral and personality measures. These measures included eating behavior (based on the *Three-Factor Eating Questionnaire*; Stunkard and Messick, 1985), sensitivity to reward and punishment (based on the *Behavioral Inhibition System/Behavioral Activation System* (*BIS/BAS*) *scales*) (Carver and White, 1994) and self-reported impulsivity (based on the *Barratt Impulsiveness Scale-11*; Patton et al., 1995). We found an inverted U-shaped relationship between restrained eating and BMI. This relationship was moderated by the level of disinhibited eating. Independent of eating behavior, *BIS* and *BAS* responsiveness were associated with BMI in a gender-specific manner with negative relationships for men and positive relationships for women. Together, eating behavior and *BIS/BAS* responsiveness accounted for a substantial proportion of BMI variance (men: ∼25%, women: ∼32%). A direct relationship between self-reported impulsivity and BMI was not observed. In summary, our results demonstrate a system of linear and non-linear relationships between the investigated factors and BMI. Moreover, body weight status was not only associated with eating behavior (*cognitive restraint* and *disinhibition*), but also with personality factors not inherently related to an eating context (*BIS/BAS*). Importantly, these relationships differ between men and women.

Keywords: eating behavior, gender differences, obesity, personality traits, reward sensitivity, punishment sensitivity, Behavioral Activation System, Behavioral Inhibition System

INTRODUCTION

Body weight regulation and the development of obesity are associated with multiple interdependent factors and mechanisms. These mechanisms include, at the individual level, genetic and endocrine factors as well as behavioral and personality characteristics (e.g., Williamson et al., 1995; Bellisle et al., 2004; Provencher et al., 2004; Dina et al., 2007; Farooqi et al., 2007; Frayling et al., 2007; Klok et al., 2007; Ahima, 2008; Davis and Fox, 2008; Rosenbaum et al., 2008; Page et al., 2011). One of the most important factors contributing to body weight status is eating behavior, which is commonly assessed by the *Three-Factor Eating Questionnaire* (*TFEQ*; Stunkard and Messick, 1985). The *TFEQ* measures three dimensions of eating behavior: *cognitive restraint (CR)*, *disinhibition (DIS)*, and *susceptibility to hunger* or *hunger (HUN)*, for short. *Cognitive restraint* measures individual control over eating. Restrained eaters attempt to suppress impulses to eat in order to pursue long-term weight goals. Typical characteristics are avoidance of fattening foods and eating of small portions. The factor *disinhibition* reflects overeating tendencies. Disinhibited eaters typically initiate eating because of external environmental cues, such as palatable food. They have difficulties resisting food stimulation and/or eat under emotional distress. Considering this, *cognitive restraint* (conscious restriction of food intake) and *disinhibition* (tendency to overeat) conceptually represent antagonistic concepts. The third factor, *hunger*, characterizes the extent to which hunger feelings are experienced and evoke food intake. While *hunger* and *disinhibition* are positively associated with body mass index (BMI; e.g., Bond et al., 2001; Boschi et al., 2001; Bellisle et al., 2004; Bryant et al., 2008; Lesdéma et al., 2012), the relationship of *cognitive restraint* and BMI seems to be more complex and non-linear: In normal weight individuals they are usually positively associated, but the relationship is typically negative in overweight and obese individuals (e.g., Foster et al., 1998; Lluch et al., 2000; Bellisle et al., 2004; Provencher et al., 2004; de Lauzon-Guillain et al., 2006; Cappelleri et al., 2009). Additionally, *cognitive restraint* and *disinhibition* are not independently related to BMI, they interactively influence body weight status (Stunkard and Messick, 1985; Westenhoefer et al., 1990; Williamson et al., 1995; Hays et al., 2002; Dykes et al., 2004). Specifically, *cognitive restraint* attenuates the effect of *disinhibition* on BMI. What is more, previous investigations indicate that eating behavior (including presumably also underlying biological mechanisms) and body weight status mutually influence each other. For example, there are alterations in the level of *cognitive restraint* as well as *disinhibition* in response to dieting (e.g., Karlsson et al., 1994; Pekkarinen et al., 1996; Foster et al., 1998; Westerterp-Plantenga et al., 1998; Dalle Grave et al., 2009; Savage et al., 2009; Tucker and Bates, 2009).

In addition to eating behavior, various personality traits are related to food consumption and weight status (Faith et al., 2001; Elfhag and Morey, 2008). One of the most popular models of personality that may explain individual variations in food intake is the *reinforcement sensitivity theory* (RST; Gray, 1970, 1982, 1987; Gray and McNaughton, 2000). Based on this theory, two general motivational systems that underlie behavior and affect have been suggested—the Behavioral Inhibition System (BIS) and the Behavioral Activation System (BAS), commonly assessed by the *BIS/BAS* scales (Carver and White, 1994). The BIS represents the aversive motivational system. It is sensitive to signals of punishment, reward omission, and novelty. The BIS is supposed to inhibit behavior that may lead to negative or painful outcomes and is associated with negative affect (negative reinforcement). The BAS reflects the appetitive motivational system. It is sensitive to signals of reward and the avoidance of punishment (positive reinforcement). High BAS responsiveness is related to enhanced approach behavior and positive affect.

As food can be both a positive or negative reinforcer, responsiveness of these systems potentially plays a substantial role in body weight regulation. However, the relationship between sensitivity to reward (as a facet of BAS responsiveness) and BMI has been almost exclusively investigated in women. Investigations showed positive associations of reward sensitivity with BMI and eating habits supporting weight gain (Davis et al., 2004, 2007; Franken and Muris, 2005). In addition, reward responsiveness has been related to neural responses. In particular sensitivity to reward was shown to be positively associated with neural responses to pictures of highly palatable food in a fronto-striatal-amygdala network (Beaver et al., 2006). Further findings indicate that long-lasting overeating and obesity account for adaptations of the reward system (Wang et al., 2001; Volkow et al., 2008; de Weijer et al., 2011). In combination with the aforementioned findings, these studies led to the development of a *hyper- vs. hyposensitivity theory* of reward in obesity (e.g., Davis and Fox, 2008). According to this theory, some individuals show an inherent heightened reward sensitivity (*hypersensitivity*) and are particularly susceptible to the rewarding properties of high-calorie food. They are thus supposed to regularly overeat on fattening food and consequently become overweight or obese. Prolonged overeating and corresponding obesity, on the other hand, are associated with alterations in the dopaminergic (DA) reward circuitry, presumably to compensate for an enhanced DA tone (Wang et al., 2001; Volkow et al., 2008; de Weijer et al., 2011). These alterations are assumed to result in *hyposensitivity* to reward in obese individuals as well as in increased hedonic eating to compensate this deficiency. This theory was explored by Davis and Fox (2008). According to their model, in both genders BMI and sensitivity to reward are non-linearly associated by an inverted U-shaped relationship. More specifically, the authors reported high reward sensitivity in overweight and mildly obese participants and low reward sensitivity in morbidly obese ones. Thus, although sensitivity to reward and sensitivity to punishment are assumed to be dispositional traits rather than transient states or symptoms (Wilksch and Wade, 2009), at least sensitivity to reward seems to be flexible to a certain extent.

To our knowledge, the association between sensitivity to punishment and BMI so far has not yet been studied directly, although several studies demonstrate a relationship between sensitivity to punishment and eating disorders. Similar to obese subjects, patients suffering from bulimia nervosa and anorexia nervosa (binge/purge subtype) are characterized by overeating. This points at possible similarities in the underlying personality structure leading to a shared decision-making profile (Brogan et al., 2010). Studies investigating eating disorders repeatedly report high punishment responsiveness in patients compared to healthy controls (e.g., Harrison et al., 2010, 2011). In addition, sensitivity to punishment has been shown to be positively associated with symptoms of binge eating (Davis, 2013). Again, these studies are almost exclusively restricted to women. Matton et al. (2013) clustered adolescents with respect to reward and punishment responsiveness. Interestingly, the cluster of subjects with both high reward sensitivity and high punishment sensitivity outscored other clusters on self-reported eating problems (i.e., data regarding concerns about eating, body shape and weight as well as emotional and external eating). Although girls were more likely to belong to this cluster, effects were similar for both girls and boys. Based on these findings, Matton et al. (2013) proposed that adolescents in this cluster are especially vulnerable to the development of eating problems.

Sensitivity to reward is regarded as one aspect of the multidimensional psychological construct *impulsivity* (e.g., Guerrieri et al., 2008). Generally, impulsive behavior is rapid and rash, characterized by a lack of planning and less forethought about consequences of spontaneous actions (Moeller et al., 2001). As the term "multidimensionality" indicates, impulsivity covers several different but related concepts. The relationship to overeating is thus not straightforward. While individual differences in some aspects of impulsivity are likely to contribute to the ability to resist overeating, others may not. Various tasks that assess aspects of impulsive behavior indicate altered decision-making in overweight and obese individuals. In *Delay Discounting Tasks* or *Delay Gratification Paradigms*, for example, obese subjects in general (Rasmussen et al., 2010) or obese women in particular (Weller et al., 2008; Weygandt et al., 2013) chose more often immediate but smaller monetary or food-related reward in comparison to normal weight control subjects. In the *Iowa Gambling Task* obese volunteers preferred high immediate reward despite long-term losses. This was shown in both genders (Pignatti et al., 2006; Brogan et al., 2011), women (Horstmann et al., 2011), or men (Koritzky et al., 2012). In addition, obese women and children of both genders lacked appropriate inhibitory control in the non-reward related *Stop Signal Task* (Nederkoorn et al., 2006a,b). Another task measuring inhibitory control, the *Go/No-Go Task*, showed especially overweight and obese adolescent girls to have difficulties inhibiting prepotent motor responses to high-calorie food (Batterink et al., 2010). Heightened impulsivity was also reported for overweight children (Braet et al., 2007) as well as overweight and obese adults (e.g., Chalmers et al., 1990; Mobbs et al., 2010) based on different self-reported measures. For example, Mobbs et al. (2010) reported higher levels of urgency, lack of perseverance and strong sensitivity to reward in overweight and obese women. They concluded that overweight and obesity are associated with problems in inhibiting dominant behavior and intrusive thoughts. Within the obese population, there is evidence for heightened self-reported impulsivity among severely compared to less severely obese individuals (Rydén et al., 2003), and impulsivity was further related to higher food intake in women using the *Barratt Impulsiveness Scale* (BIS; Guerrieri et al., 2007).

An important factor that contributes to differences in eating behavior and personality, and probably also to body weight regulation, is gender. Women, for example, have higher scores of *cognitive restraint* and *disinhibition* compared to men (Bellisle et al., 2004; Provencher et al., 2004; Li et al., 2012). Additionally, eating disorder symptomatology is more prevalent among women (e.g., Keel et al., 2007; Matton et al., 2013; Yean et al., 2013). Furthermore, men and women differ in personality traits such as impulsivity. For example, higher sensation seeking and behavioral risk taking was observed in men compared to women (Arnett, 1992; Byrnes et al., 1999; Cross et al., 2011). Additionally, both gender-independent and gender-specific effects have been reported, for example, with respect to the *Iowa Gambling Task* and weight status (Pignatti et al., 2006; Brogan et al., 2011; Horstmann et al., 2011; Koritzky et al., 2012). The precise relationship between impulsivity, BMI and gender thus is not clear from previous data. Furthermore, women are more sensitive to both reward and punishment compared to men (Carver and White, 1994; Jorm et al., 1999; Cross et al., 2011). Yet, the relationship of these measures to weight status has not been sufficiently explored in males, as described earlier. Differences in the hormonal repertoire between men and women might account for variations in the susceptibility to reinforcers like food. Ovarian hormones in particular, which affect mesolimbic DA system (i.e., reward processing; Sofuoglu et al., 1999; Kaasinen et al., 2001; Evans et al., 2002; Lynch et al., 2002; Carroll et al., 2004) but also HPA functioning (i.e., stress response; Burgess and Handa, 1992; Handa et al., 1994; Patchev et al., 1995; Young, 1995), might be responsible for such differences, making women generally more vulnerable to the reinforcing properties of most drugs of abuse (see Fattore et al., 2008, 2009 for review). As addiction and obesity share several properties (see Volkow et al., 2013 for review), there might be also gender differences in the susceptibility to the reinforcing value of food. For other personality domains and their association with weight status, the gender interaction has already been shown. In a study by Faith et al. (2001) BMI was positively associated with neuroticism and negatively with extraversion in women. In men, BMI was positively associated with extraversion and psychoticism (Faith et al., 2001). Finally, gender moderates obesity-related differences in brain structure. Specifically for women obesity-related variation were observed in regions involved in habitual and goal-directed control of behavior such as the dorsal striatum and dorsolateral prefrontal cortex (Horstmann et al., 2011).

Therapeutic approaches to obesity classically target aspects of eating behavior. Behavioral interventions, for example, aim at increasing *cognitive restraint* and decreasing *disinhibition* (e.g., Jubbin and Rajesh, 2012). Yet, as described above, individual body weight status is also related to personality traits. For a more effective treatment of obesity it is therefore necessary to regard personality traits as well. This study aims to establish a comprehensive model relating BMI to eating behavior and the most relevant obesity-related personality traits (self-reported impulsivity and reward/punishment sensitivity). We investigated questionnaire measures of these traits as they can be easily and quickly assessed in the clinical setting. *TFEQ* scales *cognitive restraint*, *disinhibition*, and *hunger* (Stunkard and Messick, 1985) served as measures of eating behavior. The *BIS/BAS* scales (Carver and White, 1994) were considered as measures of sensitivity to punishment (*BIS*) and sensitivity to reward (*BAS*). Further, self-reported impulsivity, assessed by the *BIS-11* (Patton et al., 1995), was incorporated into the model. The overall goal of our approach was to quantify the individual and joint contribution of these scales to BMI variance explanation.

Based on previous findings, different models were developed to test the following hypotheses:

(1) A significant proportion of BMI variance is explained by *disinhibition*, *hunger*, and *cognitive restraint*. According to previous findings, we assumed positive linear associations of both *disinhibition* and *hunger* with BMI (e.g., Bond et al., 2001; Boschi et al., 2001; Bellisle et al., 2004; Bryant et al., 2008; Lesdéma et al., 2012). As *cognitive restraint* and BMI are positively associated in normal weight individuals and negatively in overweight and obese individuals (e.g., Foster et al., 1998; Lluch et al., 2000; Bellisle et al., 2004; Provencher et al., 2004; de Lauzon-Guillain et al., 2006; Cappelleri et al., 2009), we expected an inverted U-shaped relationship between these variables.
(2) A portion of BMI variance is explained by the interaction of *disinhibition* and *cognitive restraint*, indicated by previous studies (Stunkard and Messick, 1985; Westenhoefer et al., 1990; Williamson et al., 1995; Hays et al., 2002; Dykes et al., 2004).
(3) Additional BMI variance is explained by the level of *BIS* (as a measure of punishment responsiveness) and *BAS* (as a measure of reward responsiveness). Based on previous research, we expected positive linear associations for both variables with BMI in women (Davis et al., 2004, 2007; Franken and Muris, 2005; Harrison et al., 2010, 2011). Despite the lack of previous data for these relationships in men, we expect the positive relationships between *BIS/BAS* and BMI to be specific for women, which is based on gender-dependent differences in the hormonal repertoire influencing the vulnerability to reinforcers (e.g., Sofuoglu et al., 1999; Kaasinen et al., 2001; Evans et al., 2002; Lynch et al., 2002; Carroll et al., 2004).

(4) Further, BMI variance is explained by the level of self-reported impulsivity (*BIS-11*). According to previous findings, we expected a positive linear association with BMI (e.g., Chalmers et al., 1990; Rydén et al., 2003; Mobbs et al., 2010). Considering opposing findings with respect to gender (Pignatti et al., 2006; Brogan et al., 2011; Horstmann et al., 2011; Koritzky et al., 2012), we tested for gender interactions, although they were not expected.

Besides the study's main purpose of modeling BMI, we had two secondary objectives:

(5) *Cognitive restraint*, *disinhibition*, and body weight status mutually influence each other (e.g., Karlsson et al., 1994; Pekkarinen et al., 1996; Foster et al., 1998; Westerterp-Plantenga et al., 1998; Dalle Grave et al., 2009; Savage et al., 2009; Tucker and Bates, 2009). Therefore, we hypothesized the quadratic relationship between BMI and *cognitive restraint* to be moderated by *disinhibition*. Depending on the level of *disinhibition*, we expected the association of BMI and *cognitive restraint* to be as follows: Normal body weight and low *disinhibition* is associated with low *cognitive restraint*. Normal body weight and high *disinhibition* is associated with high *cognitive restraint*. Overweight is associated with high *cognitive restraint* regardless of the level of *disinhibition*. Obesity is associated with low *cognitive restraint* regardless of the level of *disinhibition*.

(6) Davis and Fox (2008) demonstrated an inverted U-shaped relationship between sensitivity to reward and BMI. We aimed to corroborate these findings by testing for a quadratic relationship between *BAS* and BMI. We hypothesized an inverted U-shaped relationship between these measures.

As the focus of this investigation was on self-report questionnaires, i.e., explicit, mentally represented data, this study did not consider implicit or automatic processes (i.e., eating habits) that influence behavior and potentially body weight independently of explicit experience (e.g., Berridge and Robinson, 2003; Finlayson et al., 2008; Papies et al., 2009; Goldstein et al., 2014).

MATERIALS AND METHODS

SUBJECTS

Data were collected by the joint obesity work group of the Max Planck Institute for Human Cognitive and Brain Sciences and the IFB Adiposity Diseases in Leipzig between 2009 and 2013. Healthy adult subjects were invited to participate in different behavioral and neurocognitive experiments in the context of obesity research and were reimbursed for their participation. As part of these experiments, subjects completed various questionnaires this cross-sectional study is based on. Exclusion criteria were age under 18 or over 50 years, BMI under 18 kg/m^2, hypertension, dyslipidemia, metabolic syndrome, depression (Beck's Depression Inventory, cut-off value 18), a history of neuropsychiatric diseases, smoking, diabetes mellitus, vegetarianism, and pregnancy. Although there were no restrictions for ethnicity, only Caucasian subjects volunteered. Age in years and BMI were assessed at the time of the experiment. Height and weight for BMI calculations were measured by scientific staff at the Max Planck Institute in Leipzig. As not all questionnaires were assessed for all participants, we decided to investigate two cohorts (called *TFEQ-only* and *TFEQ-plus* cohort). The total cohort consisted of 326 healthy subjects (*TFEQ-only* cohort; 145 women, 181 men). Besides BMI, age, and gender, the *TFEQ* scores of *CR*, *DIS*, and *HUN* were assessed in these subjects. In a subgroup of 192 participants, *BIS*, *BAS*, and *BIS-11* were additionally assessed (*TFEQ-plus* cohort; 92 women, 110 men). **Table 1** depicts descriptive statistics of the two cohorts. The study was carried out in accordance with the Declaration of Helsinki and approved by the local ethics committee of the University of Leipzig. All subjects gave written informed consent before participation.

Table 1 | Descriptive statistics.

Variable	*n*	Mean (SD)	Range	Mean women (SD)	Mean men (SD)
BMI	326	26.6 (6.1)	18.1–46.5	26.4 (6.6)	26.7 (5.6)
	192	26.7 (6.2)	18.1–46.5	26.6 (6.5)	26.8 (6.0)
Age	326	26.7 (4.8)	18–46	26.3 (4.8)	27.0 (4.9)
	192	26.6 (4.7)	18–46	25.7 (4.1)	27.2 (5.0)
CR	326	6.5 (4.6)	0–19	7.3 (5.0)	5.8 (4.1)
	192	6.7 (4.7)	0–19	7.4 (5.0)	6.2 (4.4)
DIS	326	6.1 (3.2)	0–15	6.8 (3.5)	5.6 (2.8)
	192	6.1 (3.0)	1–14	6.8 (3.3)	5.6 (2.6)
HUN	326	5.5 (3.3)	0–14	5.6 (3.3)	5.5 (3.3)
	192	5.6 (3.3)	0–14	5.9 (3.4)	5.4 (3.3)
BAS	192	30.9 (8.8)	13–51	29.7 (8.5)	31.8 (9.0)
BIS	192	17.0 (3.9)	5–26	16.5 (4.3)	17.4 (3.4)
BIS-11	192	32.2 (8.7)	9–58	32.0 (8.8)	32.3 (8.6)

Descriptive statistics of variables assessed in the TFEQ-only cohort (n = 326, 145 women, 181 men) and the TFEQ-plus cohort (subgroup of TFEQ-only cohort (grey), n = 192, 82 women, 110 men). CR, TFEQ cognitive restraint score; DIS, TFEQ disinhibition score; HUN, TFEQ hunger score; BIS-11, Barratt Impulsiveness Scale 11 total score; BAS, Behavioral Activation System total score; BIS, Behavioral Inhibition System total score; TFEQ, Three-Factor Eating Questionnaire.

QUESTIONNAIRES

Three-Factor Eating Questionnaire (Stunkard and Messick, 1985; German version: Pudel and Westenhoefer, 1989)

The TFEQ is a 51-item self-report assessment of eating behavior. The questionnaire contains three subscales. The 21-item *cognitive restraint* scale (*CR*, scale range: 0–21, Cronbachs Alpha of German version = 0.84) measures intent to control food intake. The 16-item *disinhibition* scale (*DIS*, scale range: 0–16, Cronbachs Alpha of German version = 0.75) quantifies overeating tendencies. The 14-item susceptibility to *hunger* scale (*HUN*, scale range: 0–14, Cronbachs Alpha of German version = 0.76) is a measure for food intake in response to feelings of hunger.

The Behavioral Inhibition System/Behavioral Activation System Scales (Carver and White, 1994; German version: Strobel et al., 2001)

This self-report questionnaire consists of 20 items designed to assess the responsiveness of Gray's (1982, 1987) BAS and BIS as personality characteristics. The 7-item *BIS* scale measures reactivity of the aversive motivational system (scale range: 7–28, Cronbachs Alpha of German version = 0.78), whereas the 13-item *BAS* scale measures reactivity of the appetitive motivational system (scale range: 13–52, Cronbachs Alpha of German version = 0.81). The *BAS* scale can be divided into three subscales: Drive, Fun-Seeking, and Reward. In this study we applied the *BAS* sum score, as the subscales were not confirmed in the German version.

Barratt Impulsiveness Scale-11 (Patton et al., 1995; German version: Preuss et al., 2008)

The *BIS-11* is a 30-item self-report questionnaire developed to measure impulsivity. Along a four-point scale subjects rate whether statements describing impulsivity pertain to themselves (scale range: 0–90, Cronbachs Alpha of German version = 0.69). For the original English version, six factors were identified. This originally suggested factor structure was not confirmed for the German equivalent. We therefore applied the total score of the *BIS-11*, as it shows adequate internal consistency for German-speaking regions.

STATISTICAL ANALYSES

Statistical analyses were performed using SPSS (IBM Corporation Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corporation) and the SPSS toolbox PROCESS (Hayes, 2013). Associations between BMI and self-reported behavioral data were explored by means of multiple regression analyses. All variables except gender were treated as continuous variables. We separately tested for the association between the three *TFEQ* scales and BMI in the *TFEQ-only* cohort (see Association of the TFEQ Scales with BMI). Age and gender were included as covariates. Significant terms were subsequently used to build a regression model for BMI to assess the proportion of variance solely explained by variables of eating behavior (see BMI Modeling Based on the TFEQ Scales Cognitive Restraint and Disinhibition). Next, we tested *BIS-11*, *BIS*, and *BAS* seperately for their association with BMI in the *TFEQ-plus* cohort (see Association of the Barratt Impulsiveness Scale-11, Behavioral Activation System, and Behavioral Inhibition System Scales with BMI). Additionally, gender interactions for the relationships of the latter three scores with BMI were tested. Age and gender were included as covariates. Again, all significant terms were used to build a comprehensive regression model for BMI including eating behavior and personality traits (see BMI Modeling Based on Cognitive Restraint, Disinhibition, the Behavioral Activation System, and Behavioral Inhibition System Score).

Based on findings of previous studies, quadratic relationships between BMI and *CR* (moderated by *DIS*, see Interactions between Cognitive Restraint, Disinhibition, and BMI) and between BMI and *BAS* (see Quadratic Relationship between BMI and the Behavioral Activation System Score) were tested (Foster et al., 1998; Lluch et al., 2000; Bellisle et al., 2004; Provencher et al., 2004; de Lauzon-Guillain et al., 2006; Davis and Fox, 2008; Cappelleri et al., 2009). BMI was treated as regressor for these analyses.

Table 2 | Regression models and corresponding variables.

Association with regressand	Variables in model	Tested gender interaction
Linear	A, g, a	A*g
Quadratic (e.g., CR^2)	A, A^2, g, a	A^2*g
2-way interaction (DIS*CR)	A, B, A*B, g, a	–
Quadratic 2-way interaction (BMI^2*DIS)	A, B, A^2, A*B, A^2*B, g, a	–

Different regression models were computed to test our individual hypotheses. Corresponding variables of all the investigated models are listed. Partial correlations of the underlined terms were tested against 0. A, B: tested variables, e.g., Three-Factor Eating Questionnaire cognitive restraint (CR) or disinhibition score (DIS); g, gender; a, age.

Table 2 lists the regression models which were used to test all abovementioned associations. As measures of effect size we used partial correlations and squared partial correlations. The latter can be interpreted as the regressand's (e.g., BMI) proportion of variance which can be explained by a single regressor (e.g., *DIS*) when all other variables are held constant. For reasons of consistency, not to indicate causality, BMI was depicted at the x-axis of every graph. We added a table of Pearson Correlations of the assessed variables at the end of the results section (see Pearson Correlations of All Variables of Interest).

RESULTS

TFEQ-ONLY COHORT ($n = 326$)

Association of the Three-Factor Eating Questionnaire scales with BMI

In the total cohort of 326 subjects, a gender difference in *CR* ($p = 0.004$) and in *DIS* ($p = 0.001$) was observed, with women having higher scores in both cases. BMI significantly correlated with *DIS*, CR^2 (hypothesis 1), and the interaction term of *CR* and *DIS* (hypothesis 2; **Figure 1**; partial correlations, all $p < 0.0005$; see **Table 3**). We observed no significant association of *HUN* with BMI.

BMI modeling based on the TFEQ scales cognitive restraint and disinhibition

To obtain a model for BMI regressed on the *TFEQ* scales, a multiple regression analysis using all former significant terms (i.e., *CR*, *DIS*, CR^2, and *CR** *DIS*; additional covariates age and gender) was conducted. The underlying adjusted R^2 of this model was 0.232 (women: 0.247, men: 0.208). *CR** *DIS* as well as CR^2 separately explained part of BMI variance, as their partial correlations differed from 0 (both $p < 0.0005$). Hence, the *TFEQ* scales *CR* and *DIS* (in addition to age and gender) explained about 23% of the overall variance of BMI in the population of this cohort.

Interactions between cognitive restraint, disinhibition, and BMI

We hypothesized a quadratic relationship between *CR* and BMI (hypothesis 5). The regression of *CR* on BMI^2 confirmed this hypothesis (squared partial correlation: 0.029, $p = 0.002$, age and gender as covariates). Furthermore, this inverted U-shaped

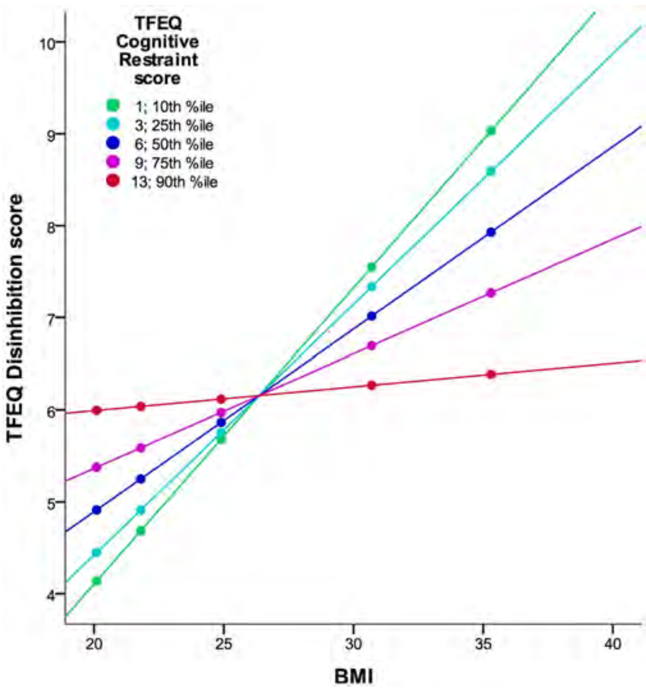

FIGURE 1 | Interaction of DIS and CR on BMI in the TFEQ-only cohort ($n = 326$). The figure illustrates the linear relationship between BMI and DIS moderated by the level of CR with age and gender as covariates. Partial correlation of BMI*CR is −0.203 ($p < 0.0005$; adjusted R^2 change of 0.163 through BMI, CR, and BMI*CR). Dots indicate 10th, 25th, 50th, 75th, and 90th percentiles of BMI (20.1, 21.8, 24.9, 30.7, and 35.3 kg/m^2). Colors indicate 10th, 25th, 50th, 75th, and 90th percentiles of CR (1, 3, 6, 9, 13). CR, cognitive restraint score; DIS, disinhibition score; TFEQ, Three-Factor Eating Questionnaire.

relationship was moderated by *DIS* ($p = 0.001$). In other words, the relationship between BMI and *CR* differed with respect to the *DIS* score (**Figure 2**): For low *DIS* scores the quadratic association between *CR* and BMI was well pronounced, whereas no strong quadratic relationship for high *DIS* scores was observed.

TFEQ-PLUS COHORT ($n = 192$)

Association of the Barratt Impulsiveness Scale-11, Behavioral Activation System, and Behavioral Inhibition System Scales with BMI

With respect to eating behavior (based on the *TFEQ*), results in the subgroup of 192 participants (*TFEQ-plus* cohort) were comparable with the whole sample (*TFEQ-only* cohort, $n = 326$).

BAS and *BIS* scores did not correlate with BMI, but showed a significant interaction with gender (hypothesis 3; all $p = 0.001$). In women, there was a significant positive correlation of *BIS* and BMI (partial correlation = 0.281; $p = 0.011$) as well as a strong tendency for the correlation of *BAS* and BMI (partial correlation = 0.214; $p = 0.055$). In men, we found a significant negative correlation of *BIS* and BMI (partial correlation = −0.208; $p = 0.03$) as well as *BAS* and BMI (partial correlation = −0.295; $p = 0.002$). The relationship of BMI and *BAS*, moderated by gender, is shown in **Figure 3** (results for the association of *BIS* and BMI are comparable). Concerning the association of self-reported impulsivity and BMI, neither a correlation between BMI and *BIS-11* (total score) nor a gender interaction was found (hypothesis 4).

Table 3 | Squared partial correlations (SPC) with BMI.

Variable	Squared partial correlation (η_p^2)	Direction of correlation	*p*-value
CR	(0.009)	(+)	0.083
DIS	0.138	+	<0.0005
HUN	(0.003)	(+)	0.596
CR^2	0.054	−	<0.0005
CR*DIS	0.054	−	<0.0005

Squared partial correlations with BMI in the TFEQ-only cohort (n = 326) in a regression model with age and gender as covariates. SPC can be interpreted as the proportion of BMI variance explained only by the corresponding variable, not by covariables. CR, TFEQ cognitive restraint score; DIS, TFEQ disinhibition score; HUN, TFEQ hunger score; TFEQ, Three-Factor Eating Questionnaire.

BMI modeling based on cognitive restraint, disinhibition, the Behavioral Activation System, and Behavioral Inhibition System score

The final model comprised the relevant variables of self-reported eating behavior (see BMI Modeling based on the TFEQ Scales Cognitive Restraint and Disinhibition, *TFEQ-only* model) as well as *BIS*, *BAS*, gender, *BIS**gender, *BAS**gender and age as regressors. The resulting adjusted R^2 was 0.271 (women: 0.324, men: 0.252). R^2 for women and men did not differ significantly ($p = 0.474$, two-tailed Fisher's Z). Independent of eating behavior, *BIS* and *BAS* significantly contributed to variance explanation of BMI (R^2 change of *TFEQ-only* model and *TFEQ-plus* model in the sample of $n = 192$, $p < 0.0005$). Hence, self-reported behavioral measures of *CR*, *DIS*, *BIS*, and *BAS* in addition to age and gender explained about 27% of the overall variance of BMI in the population of this sample. See **Figure 4** for variance proportions of the variables for each gender.

Quadratic relationship between BMI and the Behavioral Activation System score

As Davis and Fox (2008) reported an inverted U-shaped association between sensitivity to reward and BMI, we tested for the quadratic association of *BAS* with BMI (hypothesis 6). We corroborated their finding: BMI showed a quadratic relationship with *BAS* ($p = 0.018$, age and gender as covariates, adjusted R^2 changed by 0.03 after adding BMI and BMI^2). There was only a trend for a gender interaction of this effect ($p = 0.091$, stronger effect in women). Concerning the model, a BMI of around 30 kg/m^2 was associated with the highest *BAS* scores, whereas a higher and lower BMI was associated with lower *BAS* scores (**Figure 5**).

PEARSON CORRELATIONS OF ALL VARIABLES OF INTEREST

For an overview of the assessed variables and how they are interrelated, see **Table 4**. As the correlation of *BIS* and *BAS* was not

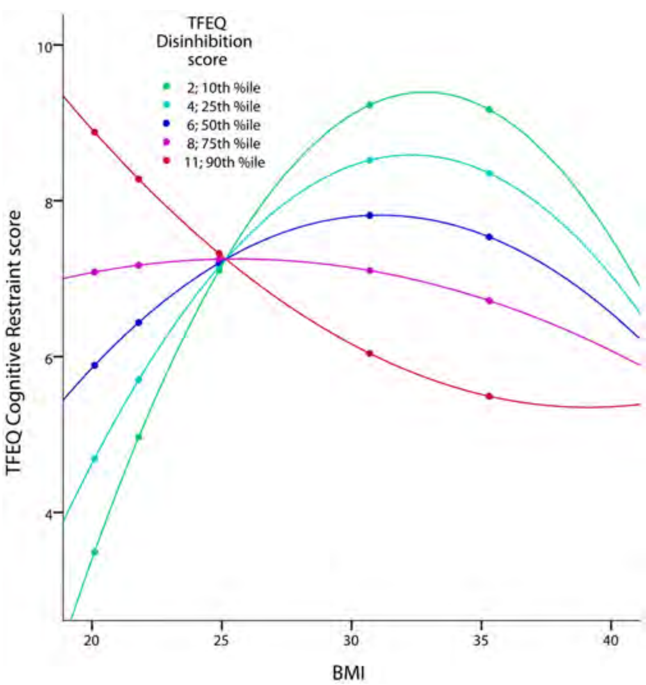

FIGURE 2 | Quadratic interaction of BMI and DIS on CR in the TFEQ-only cohort ($n = 326$). The figure illustrates the quadratic relationship between BMI and CR moderated by the level of DIS with age and gender as covariates. Partial correlation of BMI^2*DIS is 0.185 ($p < 0.001$; adjusted R^2 change of 0.083 through BMI, DIS, BMI^2, BMI*DIS and BMI^2*DIS). Dots indicate 10th, 25th, 50th, 75th, and 90th percentile of BMI (20.1, 21.8, 24.9, 30.7, and 35.3 kg/m^2). Colors indicate10th, 25th, 50th, 75th, and 90th percentiles of CR (2, 4, 6, 8, 10). CR, cognitive restraint score; DIS, disinhibition score; TFEQ, Three-Factor Eating Questionnaire.

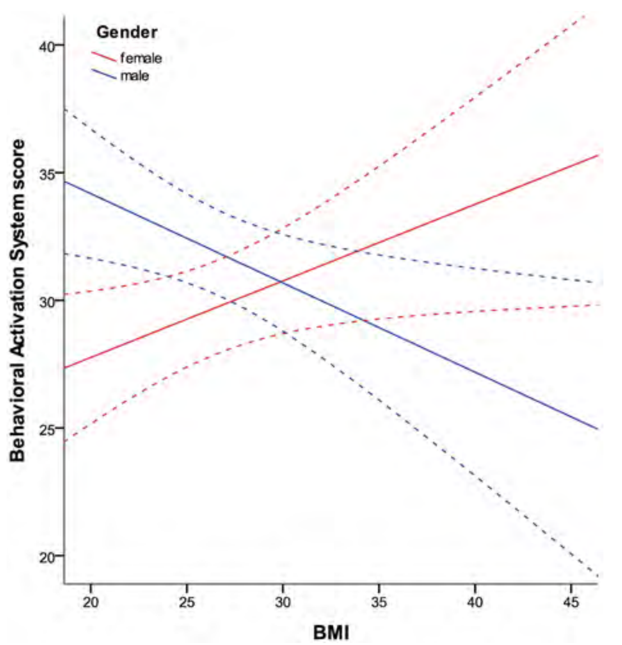

FIGURE 3 | Relationship between BMI and BAS in women and men in the TFEQ-plus cohort ($n = 192$). As the relationship of BAS and BMI is moderated by gender, it is shown separately. Partial correlation of BMI*gender is −0.255 ($p < 0.0005$, age as covariate). Partial correlation of BMI (age as covariate) with BAS is 0.214 in women ($n = 82$) and −0.295 in men ($n = 110$). Dashed lines indicate confidence interval of 95% for the fit lines. BAS, Behavioral Activation System total score.

described thus far, this association was further investigated. One reason for this relationship might be the high proportion of obese subjects in our sample. Therefore we tested for an interaction of BMI with *BIS* or *BAS*. Also gender interactions of this assumed effects were tested. We found a 3-way-interaction between BMI, gender and *BIS* ($p = 0.007$ for *BIS**BMI*gender with *BAS* as regressand; age as covariate). Probing this 3-way-interaction revealed that women with a high BMI had a stronger association of *BIS* with *BAS*.

DISCUSSION

RELATIONSHIP BETWEEN EATING BEHAVIOR AND BMI

Interestingly, only two measures of eating behavior, *disinhibition* and *cognitive restraint*, accounted for much of BMI variance (∼23%). In other words, the individual level of overeating tendencies in interaction with the level of conscious efforts to restrict food intake explained a large amount of variance in individual body weight status. *Susceptibility to hunger* did not contribute to variance explanation of BMI. However, an association of *hunger* with *disinhibition* and *cognitive restraint* was shown in our sample, which is in line with previous studies (Bellisle et al., 2004; Lesdéma et al., 2012).

Besides modeling of BMI, we aimed to investigate the apparent non-linear relationship between *cognitive restraint* and BMI. We found an inverted U-shaped association of BMI with *cognitive restraint*. Our model demonstrates low levels of *cognitive restraint* at the outer edges of the BMI range and a high level around the overweight range. Interestingly, this relationship was moderated by the level of *disinhibition*. For low levels of *disinhibition* (low overeating tendencies) the curvilinear relationship between BMI and *cognitive restraint* was well pronounced. Accordingly, we conclude that restrained eating is low in normal weight individuals as food restriction is presumably not necessary. With higher BMI, food restriction becomes necessary, as losing weight or avoiding further weight gain are supposedly more frequent with higher BMI (maximum in the overweight/moderate obese range of the BMI). In the obese BMI range, the positive relationship between BMI and *cognitive restraint* is shifted, resulting in relatively low levels of restrained eating among morbidly obese individuals. Although restrained eating seems desirable in this BMI range, morbidly obese individuals might not be able to raise sufficient self-control resources to restrict food intake. This notion is supported by neuroimaging studies that report structural as well as functional obesity-related alterations in brain structures associated with self-control (Le et al., 2006, 2007; Horstmann et al., 2011). With higher levels of *disinhibition* there was no strong curvilinear relationship between BMI and *cognitive restraint*. This effect indicates that in response to heightened overeating tendencies, normal weight individuals increase conscious efforts to restrict food intake in order to maintain weight/stay slim. Overweight and moderately obese

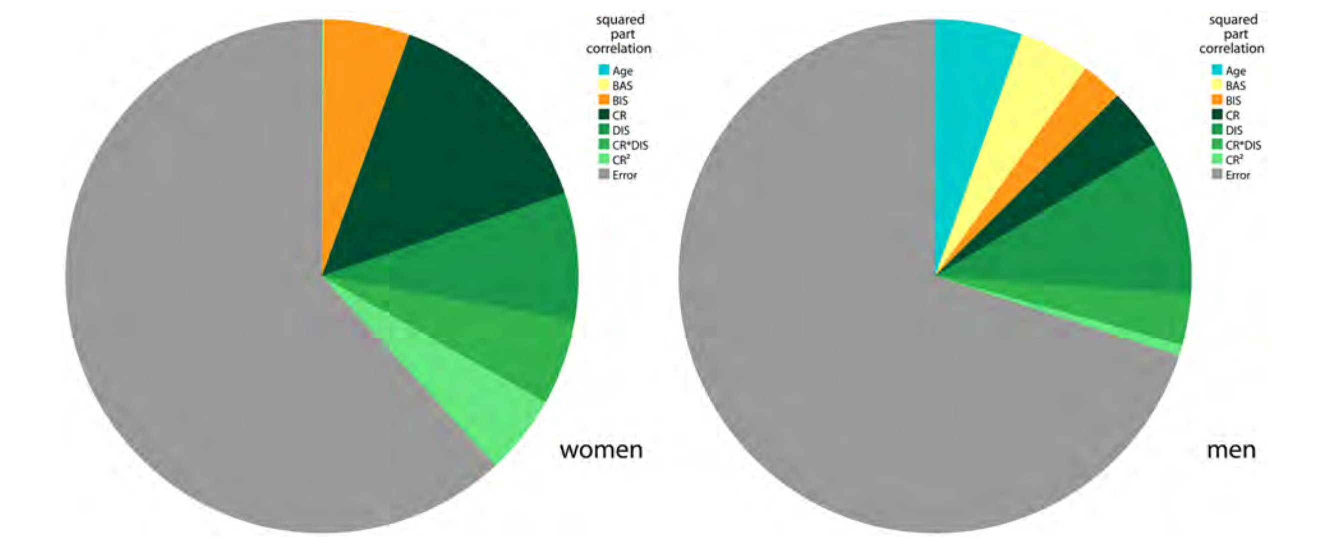

FIGURE 4 | BMI variance explained by final regression model in men and women. The pie charts show the squared part correlations of all variables of the final BMI model in the TFEQ-plus cohort ($n = 192$). All variables with significant correlation to BMI were included. As the directions of the effect of BAS and BIS differed between men and women, separate models comprising the same variables were computed. R^2 for women ($n = 82$) = 0.382. R^2 for men ($n = 110$) = 0.300. CR, TFEQ cognitive restraint score; DIS, TFEQ disinhibition score; BAS, Behavioral Activation System total score; BIS, Behavioral Inhibition System total score; TFEQ, Three-Factor Eating Questionnaire.

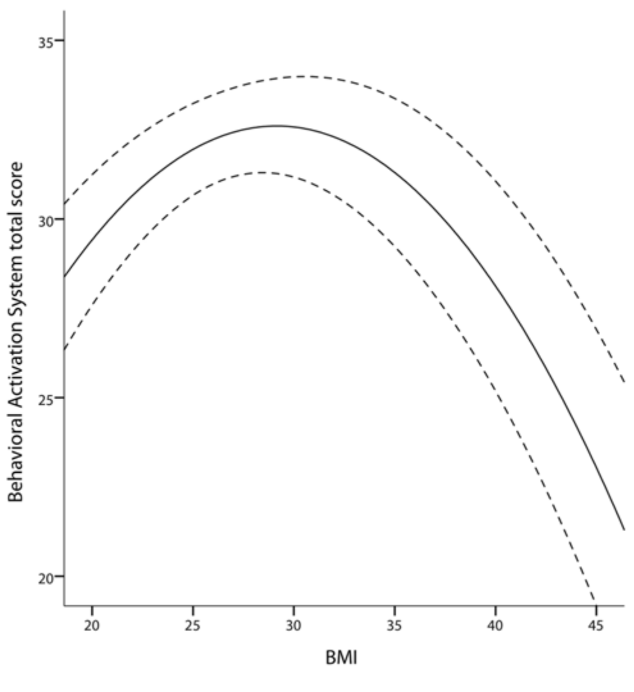

FIGURE 5 | Quadratic association between BAS and BMI in the TFEQ-plus cohort ($n = 192$). Partial correlation of BMI^2 is −0.92 ($p = 0.008$, adjusted R^2 change of 0.039 through BMI and BMI^2, age and gender as covariates). Dashed lines indicate the 95% confidence interval of the quadratic fit line. BAS, Behavioral Activation System total score.

individuals presumably do not adequately adapt their dietary restraint. On the contrary, the model indicates that attempts to restrict food intake decrease (reflected in lower levels of *cognitive restraint*) with stronger disinhibited eating. Eating behavior seems to be more and more dominated by an uncontrolled eating style, driven by, for example, external eating signals or habitual food intake.

GENDER-SPECIFIC RELATIONSHIPS BETWEEN *BIS/BAS* AND BMI

The aforementioned model for BMI based on eating behavior was extended to incorporate personality factors not inherently related to food context but potentially influencing body weight. Both *BIS* and *BAS* explained part of BMI variance independently of eating behavior (~6%), whereby they inversely accounted for BMI variance in men and women. Both scales were positively associated with BMI in women, but negatively in men.

BAS RESPONSIVENESS AND BMI

Studies already showed that reward responsiveness is positively related to body weight status and eating habits contributing to weight gain in women (Davis and Woodside, 2002; Davis et al., 2004; Franken and Muris, 2005; Loxton and Dawe, 2006). Women report more food cravings than men, indicating heightened motivation for hedonic eating (Lafay et al., 2001; Cepeda-Benito et al., 2003; Meule et al., 2012). Moreover, several studies have shown that women are highly susceptible to the sociocultural pressure resulting from the "lean ideal" portrayed by the media, leading to attempts to lose weight and be slim (Polivy and Herman, 2004; Dittmar, 2005; Mask and Blanchard, 2011; Yean et al., 2013). As a consequence food restriction and avoidance behavior might boost initial vulnerability to and incentive saliency of highly palatable "forbidden" food. In males, drive for a lean body has been shown to be lower (e.g., Cohane and Pope, 2001; Grogan and Richards, 2002; Yean et al., 2013). Their individual motivational value of food might thus be less environmentally influenced.

Table 4 | Pearson correlations.

		BIS-11	BAS	BIS	HUN	DIS
CR	*r*	−0.196**	0.180*	0.018	**−0.227*** **	0.148*
	p	0.006	0.013	0.801	**0.002**	0.041
DIS	*r*	0.046	0.135	−0.022	**0.494*** **	
	p	0.525	0.061	0.764	**<0.0005**	
HUN	*r*	0.195**	−0.050	−0.062		
	p	0.007	0.487	0.391		
BIS	*r*	−0.002	**0.324*** **			
	p	0.981	**<0.0005**			
BAS	*r*	−0.132				
	p	0.068				

**p < 0.05, **p < 0.01, ***p < 0.0033.*

*Pearson correlations between all assessed questionnaire scores in the TFEQ-plus cohort (n = 192). p-values < 0.0033 (***, bold) are considered as significant after Bonferroni correction for multiple comparison. Noticeable are the associations of CR with HUN (negative), DIS with HUN (positive), and BAS with BIS (positive) as well as the trend toward the correlation of CR and BIS-11 (negative). CR, TFEQ cognitive restraint score; DIS, TFEQ disinhibition score; HUN, TFEQ hunger score; BIS-11, Barratt Impulsiveness Scale 11 total score; BAS, Behavioral Activation System total score; BIS, Behavioral Inhibition System total score; TFEQ, Three-Factor Eating Questionnaire.*

For men, reward associated with novelty and excitement might be particularly reinforcing. Studies reported a higher risk for excitement-related addiction like pathological gambling (see van den Bos et al., 2013a for review), alcohol and cannabis (Wagner and Anthony, 2007; NSDUH, 2012; EMCDAA, 2013) or exercise dependence (Crossman et al., 1987; Pierce et al., 1997; Weik and Hale, 2009) in men.

BIS RESPONSIVENESS AND BMI

Emotional eating, which is related to punishment sensitivity (Gray, 1970, 1982, 1987), serves as a way to compensate perceived punishment/negative affect in women (van Strien et al., 1986, 2013; Geliebter and Aversa, 2003; Nolan, 2012). Therefore obesity in women with high *BIS* responsiveness might be related to compensational eating. Men generally show a lower sensitivity to punishment (Cross et al., 2011) as well as stronger emotional and cognitive control over immediate emotional events (especially punishments; van den Bos et al., 2013b), presumably reducing their need for compensation of negative emotionality. Further, there is no clear-cut link between negative emotional eating and BMI in men (Macht et al., 2002; Geliebter and Aversa, 2003; Nolan, 2012), and, in contrast to women, food craving has been associated with positive mood states (Lafay et al., 2001). In contrast to women *BIS* responsiveness in men might reflect differences in risk taking behavior. Koritzky et al. (2012) showed that particularly overweight and obese in comparison to lean men decided more often for high immediate reward despite long-term losses. Accordingly, they might more easily ignore long-term consequences of overeating, such as weight gain, because of low sensitivity to related punishment.

Although the *BIS* and *BAS* scales are assumed to be orthogonal (Gray, 1982, 1987), we found a correlation between the two measures. As BMI moderated the relationship between *BIS* and *BAS* in women, we assume that differences in body weight status accounted for this effect in our sample.

INVERTED U-SHAPED RELATIONSHIP BETWEEN BMI AND *BAS*

We corroborated the inverted U-shaped relationship between sensitivity to reward and BMI demonstrated by Davis and Fox (2008) using the *BAS* scale. Following Davis and Fox (2008), subjects with a high BMI in the non-obese range are supposed to face stronger food cravings and appetitive drive, resulting in enhanced hedonic eating, weight gain, and possibly overweight. Davis and Fox (2008) assumed that these individuals detect rewarding stimuli like palatable food more easily and more likely approach them. The inverse relationship between BMI and *BAS* in the obese range of the BMI is supposed to reflect reward deficiency resulting from hypo-DA functioning in obese individuals (Wang et al., 2001; Volkow et al., 2008; de Weijer et al., 2011). Compensatory hedonic eating probably compensate for this deficiency.

RELATIONSHIP BETWEEN SELF-REPORTED IMPULSIVITY AND BMI

The contribution of self-reported impulsivity on body weight remains vague. Impulsivity did not explain BMI variance in our dataset. Contradictory results regarding the relationship with BMI have been reported previously (Nolan, 2012; van Koningsbruggen et al., 2013). In general, none of the subscales seem to be consistently related to overeating or BMI (Meule, 2013). However, we observed a trend for a negative correlation between *BIS-11* and *cognitive restraint*. This indicates an indirect influence of impulsivity on body weight status via eating behavior, which is in line with previous findings (Leitch et al., 2013).

STUDY LIMITATIONS AND FUTURE DIRECTIONS

This study is based on analyses of self-reported measures, i.e., mentally represented, explicitly accessible information. We have not considered automatic processes (i.e., eating habits) like implicit food attitudes (e.g., Papies et al., 2009; Goldstein et al., 2014) or implicit liking/wanting (e.g., Berridge and Robinson, 2003; Finlayson et al., 2008), which should be regarded in future studies.

Furthermore, impulsivity is a multifaceted construct (e.g., Patton et al., 1995; Whiteside and Lynam, 2001). According to insufficient validity of the factor structure of the *BIS-11* in German (Preuss et al., 2008) we restricted our analysis to the *BIS-11* total score. Another impulsivity scale, the *UPPS Impulsive Behavior Scale* (Whiteside and Lynam, 2001), is recommended as an additional self-report measure of impulsivity. This scale is associated with obesity (Mobbs et al., 2010), but probably measures aspects of impulsivity that are not covered by *BIS-11* (Meule, 2013).

Moreover, *cognitive restraint* has been proposed to be subdivided into a rigid and flexible component (Westenhoefer, 1991; Westenhoefer et al., 1999). For reasons of construct validity, the *cognitive restraint* scale has been expanded by several further items (Westenhoefer et al., 1999). We recommend assessment of these items, because subscaling allows a more detailed analysis of *cognitive restraint's* influence on body weight.

Finally, BMI, although a common way to assess obesity, is a rather course measure. It relates body weight to body height without taking actual body composition into account. As it does not measure body fat directly, erroneous evaluation of body weight status with respect to obesity can occur (Rothman, 2008). Addressing this limitation, we recommend consideration of additional measures like waist/hip ratio or concentration of adipokines like leptin (Badman and Flier, 2005).

SUMMARY

This study demonstrates that responsiveness to the behavioral activation and behavioral inhibition system explains differences in BMI independently of eating behavior. Interestingly the relationships of BMI to *BIS* and *BAS* depend on gender, with opposing directions in men and women. Therefore, specified for men and women, *BIS/BAS* responsiveness should be considered in the treatment of obesity. Further, our study contributes to a better understanding of the complex relationships between eating behavior and body weight status. We showed that *cognitive restraint* and BMI are non-linearly associated (inverted U-shaped relationship). Importantly, this relationship is moderated by the level of *disinhibition.*

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ORIGINAL ARTICLE

Brain regulation of food craving: relationships with weight status and eating behavior

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OBJECTIVES: Food craving is a driving force for overeating and obesity. However, the relationship between brain mechanisms involved in its regulation and weight status is still an open issue. Gaps in the studied body mass index (BMI) distributions and focusing on linear analyses might have contributed to this lack of knowledge. Here, we investigated brain mechanisms of craving regulation using functional magnetic resonance imaging in a balanced sample including normal-weight, overweight and obese participants. We investigated associations between characteristics of obesity, eating behavior and regulatory brain function focusing on nonlinear relationships.

SUBJECTS/METHODS: Forty-three hungry female volunteers (BMI: 19.4–38.8 kg m^{-2}, mean: 27.5 ± 5.3 s.d.) were presented with visual food stimuli individually pre-rated according to tastiness and healthiness. The participants were instructed to either admit to the upcoming craving or regulate it. We analyzed the relationships between regulatory brain activity as well as functional connectivity and BMI or eating behavior (Three-Factor Eating Questionnaire, scales: Cognitive Restraint, Disinhibition).

RESULTS: During regulation, BMI correlated with brain activity in the left putamen, amygdala and insula in an inverted U-shaped manner. Functional connectivity between the putamen and the dorsolateral prefrontal cortex (dlPFC) correlated positively with BMI, whereas that of amygdala with pallidum and lingual gyrus was nonlinearly (U-shaped) associated with BMI. Disinhibition correlated negatively with the strength of functional connectivity between amygdala and dorsomedial prefrontal (dmPFC) cortex as well as caudate.

CONCLUSIONS: This study is the first to reveal quadratic relationships of food-related brain processes and BMI. Reported nonlinear associations indicate inverse relationships between regulation-related motivational processing in the range of normal weight/overweight compared with the obese range. Connectivity analyses suggest that the need for top-down (dlPFC) adjustment of striatal value representations increases with BMI, whereas the interplay of self-monitoring (dmPFC) or eating-related strategic action planning (caudate) and salience processing (amygdala) might be hampered with high Disinhibition.

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INTRODUCTION

These days obesity has become one of the major health risks of western societies.[1] A main cause of the rising obesity level is overeating in response to a food-rich environment.[2] Appetizing but high-caloric food is omnipresent and triggers craving, that is, the intense desire for certain food, which can result in overconsumption.[3] Further, heightened food craving has been linked to a higher weight status.[3] Consequently, therapeutic approaches targeting food craving are promising tools to successfully control weight.[4] To improve such treatments, it is necessary to understand the underlying brain mechanisms of food-craving regulation.

Recently, a network mediating food-related appetitive behavior consisting of neural structures commonly identified as being sensitive to food- and eating-associated stimuli has been proposed.[5] Four interconnected brain regions form the core of this network: amygdala including hippocampus, striatum, ventromedial prefrontal cortex (vmPFC) including orbitofrontal cortex and insula.[5] Activity of these areas is related to the processing of food motivation as well as food reward (anticipation or delivery),[5–8] and enhanced activity has been associated with the desire for appetizing food.[9] The core regions' activity is modulated via higher-order executive control areas including dorsal anterior cingulate cortex (dACC) and lateral prefrontal cortex.[5,10] Previous functional magnetic resonance imaging (fMRI) studies demonstrated that volitional regulation of the desire for appetizing food relates to decreased activity in the core appetitive network accompanied by heightened activity in the lateral and medial prefrontal control regions.[9,11–16]

As food craving and overeating differ with respect to weight status,[3] also neural mechanisms of craving regulation likely vary as a function thereof. Strikingly, relationships between weight status and neural correlates of food-craving regulation are still open issues. Some studies investigating neural correlates of food-craving regulation did not report on BMI effects.[9,11,12] The studies which showed relationships of weight status and brain regulation of food craving are inconsistent in that no[14,16] smaller[13,15,17] or larger[18] responses in executive control areas of the lateral prefrontal cortex have been reported with higher BMI. Reasons for that inconsistency might be manifold. To our knowledge, balanced samples of the full BMI range have been investigated in children and adolescents only.[14,15] In adults, two studies

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compared groups of normal-weight and obese participants but spared out the overweight status.[17,18] Other studies investigating BMI continuously mainly included normal-weight participants.[13,16] Moreover, none of the above-mentioned studies investigated or reported nonlinear associations with BMI. However, there is evidence for quadratic relationships between BMI and behavior. Overweight and mild obesity seem to be characterized by heightened eating-related self-control and reward sensitivity in comparison to normal weight and severe obesity.[19,20] The biological basis of these nonlinear relationships might be weight-status-associated alterations in the dopaminergic system, recently proposed to be driven by shifts in the balance between dopaminergic tone and phasic dopaminergic signals.[21] Thus, a continuous investigation of the full BMI range with a focus on quadratic relationships seems to be highly relevant to our understanding of brain mechanisms contributing to food overconsumption and the development and maintenance of obesity.

With the current study, we directly addressed this issue. By means of fMRI, we investigated neural correlates of food-craving regulation in a balanced sample of hungry normal-weight to obese women. We focused particularly on nonlinear (that is, quadratic) relationships with BMI. As dietary self-control is nonlinearly (inverted U-shaped) related to BMI,[20] we hypothesized quadratic relationships between brain activity during the regulation of food craving and BMI in areas involved in executive control and salience processing. In addition to weight status, we hypothesized characteristics of eating behavior, as assessed by the Cognitive Restraint (CR) and Disinhibition (DIS) scales of the Three-Factor Eating Questionnaire,[22] to be related to reactivity of the appetitive network. Cognitive Restraint measures conscious efforts to regulate food intake in order to achieve long-term weight goals.[22] Therefore, we hypothesized Cognitive Restraint to be related to regulatory brain activity of top-down control regions. Disinhibition assesses overeating tendencies provoked by emotional or situational triggers and is positively associated with aspects of food reward.[22,23] Thus, we hypothesized Disinhibition to scale with reward- and motivation-related brain activity. Further, previous studies demonstrated obesity-associated alterations in functional connectivity within core structures of the appetitive network or regions implicated with executive control during the presentation of palatable food cues.[17,24] Therefore, we hypothesized functional connectivity within the appetitive network and with executive control regions to be modulated by weight status and characteristics of eating behavior.

MATERIALS AND METHODS

Participants

This investigation is an extension to the study of Hollmann *et al.*[16] The prior sample ($n = 20$) of mainly normal-weight participants ($n = 17$) was extended to a balanced sample of 43 healthy normal weight to obese females (see Table 1 for detailed descriptive statistics). Volunteers were nonsmokers without indications for major depression (Beck's Depression Inventory, cutoff value 18),[25] abnormalities in the T1-weighted structural MR scan or contraindications to MRI. The participants gave written informed consent in accordance with the Declaration of Helsinki and the requirements of the local ethics committee of the University of Leipzig. Furthermore, we included only volunteers who did not exclusively follow a vegetarian diet. According to gender-related differences in the behavioral and neural responses to food, we restricted the study to women.[26] To avoid confounding effects of the menstrual cycle on appetite and the underlying neural processes, experiments were conducted in a period between the third and thirteenth day of the menstrual cycle.[27] As the response of the appetitive network to food images is greater in a hungry state,[8] volunteers were instructed to fast at least 6 h before the fMRI session that was conducted between 1400 to 2000 h. Further, volunteers completed the Three-Factor Eating Questionnaire.[22] The scales CR (range 0–21) and DIS (range 0–16) were considered for analysis.

Table 1. Descriptive statistics of the studied sample, $n = 43$ (female)

	BMI (kg m^{-2})	*DIS*	*CR*	*Age (years)*	*Craving intensity*	*Regulation success*
Range	19.4–38.8	1–14	0–15	21–36	2.1–4.0	1.7–3.5
Mean	27.5	7.49	7.0	26.7	3.5	2.7
(s.d.)	(5.3)	(3.6)	(4.0)	(3.5)	(0.4)	(0.5)

Abbreviations: BMI, body mass index; CR, Cognitive Restraint; DIS, Disinhibition.

Experimental paradigm

Before the fMRI experiment, each participant rated 180 high-caloric food images according to tastiness and healthiness. For each participant, 60 pictures individually rated as 'unhealthy' were chosen as stimuli for the fMRI task—30 images rated as tasty and 30 images rated as not tasty. During the fMRI task, we presented the volunteers with every food picture for 6 s under two conditions. During the 'ADMIT' condition, the participants were instructed to freely crave for the following three presented food pictures. In the 'REGULATE' condition, the participants were instructed to downregulate their craving for the following three food images using everyday mental strategies. The participants were asked about individual strategy use at the end of the fMRI session. After every trial (series of three food pictures), the participants rated their performance by pressing one of four buttons inside the scanner (Figure 1). Rating of 'ADMIT' trials was considered as a measure of individual craving intensity, whereas it was regarded as a measure of subjective regulation success in 'REGULATE' trials. Ratings of craving intensity and regulation success were averaged, respectively. Please see ref. 16 for additional details on the paradigm.

Imaging procedure

A 3 T whole-body MRI scanner (TIM Trio; Siemens Medical Systems, Erlangen, Germany) was used to measure the blood-oxygen-level dependent (BOLD) signal during the above-presented experimental paradigm. We followed the imaging procedure described in ref. 16.

Data analysis

The analysis was based on SPM 8 (Wellcome Department of Imaging Neuroscience, London, UK) and Matlab 2010b (http://www.mathworks.com/). Pre-processing of the imaging data consisted of time-acquisition correction to the slice obtained at TR/2, motion correction and normalization to the standard MNI (Montreal Neurological Institute) template brain using individual high-resolution T1-weighted structural images,

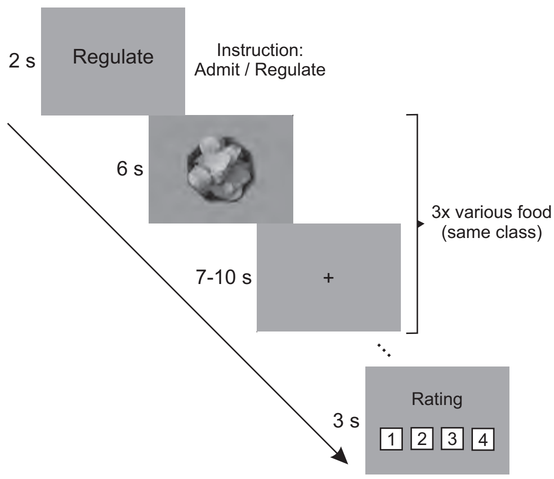

Figure 1. Design of a trial of the fMRI session. The instruction 'Admit' or 'Regulate' referred to the three following food items. According to individual pre-ratings, pictures of one trial belonged either to the class 'tasty' or 'not tasty'. After each trial, participants rated their performance (corresponds to craving intensity or regulation success) on a scale of 1–4 via button-press inside the scanner.

which resulted in a voxel size of $3 \times 3 \times 3$ mm^3. Functional images were high-pass-filtered (filter size 128 s) and spatially smoothed according to an 8 mm isotropic Gaussian kernel.

Analysis of BOLD response. On the single-subject level, a general linear model was defined including the regressors REGULATE_TASTY, REGULATE_NOT_TASTY, ADMIT_TASTY and ADMIT_NOT_TASTY. The regressors were convolved with a double-gamma hemodynamic response model. We investigated the BOLD response during the epoch of 6 s during which food images were presented. Re-alignment parameters were added as nuisance regressors to account for residual motion effects. The resulting general linear model was corrected for temporal autocorrelation using a first-order autoregressive model. Second-level analysis was based on the contrast estimates of the first-level analysis. To compare this study with previous findings and demonstrate its conceptual validity, main effects of regulation and tastiness as well as corresponding interactions were investigated across all subjects (please see the Supplementary section II for details).

Our main goal was to identify associations (linear and quadratic) of BMI and characteristics of eating behavior (CR, DIS) with BOLD activation during volitional regulation of food craving. We tested separate regression models to individually assess the relationship of BMI, CR, DIS or regulation success and the respective regulation contrasts (REGULATE_TASTY > ADMIT_TASTY, REGULATE_TASTY > REGULATE_NOT_TASTY) including age (analyses of BMI, CR, DIS, regulation success) or age and BMI (analysis of BMI^2) as covariates. To assess the relationship of craving intensity and appetitive brain activity, separate regression models were tested on the respective craving contrasts (ADMIT_TASTY > REGULATE_TASTY, ADMIT_TASTY > ADMIT_NOT_TASTY). Please see Supplementary Table III for a summary of performed regression analyses. Second-level maps were thresholded voxelwise at $P < 0.001$ and corrected for multiple comparisons at a cluster threshold of $P < 0.05$ (family-wise error) for the whole brain.

Functional connectivity analysis. Functional connectivity was assessed by means of psychophysiological interaction (PPI) analysis.[28] Source regions were based on the above-mentioned regression analysis of BOLD activation and BMI, our primary research focus. Individual BOLD signal time series within 4-mm spheres surrounding detected peak coordinates were extracted (based on the inverted U-shaped relationship of BMI and REGULATE_TASTY > ADMIT_TASTY, please see 'Results' section and Table 2 for details). General linear models were estimated separately for every source region including the following regressors: Time course of the respective source region (physiological vector), a vector coding for the main effect (psychological vector; REGULATE_TASTY > ADMIT_TASTY; with the former term weighted as +1 and the latter one weighted as − 1), and the PPI term (element-by-element product between the time course of the source region and the vector coding the main effect). The models also included realignment parameters as nuisance regressors. Single-subject contrasts for the PPI regressors were calculated. In the second-level analysis, we aimed to identify regions whose functional connectivity was related to BMI (linear and quadratic) or characteristics of eating behavior (CR, DIS). Therefore, the PPI terms were regressed on these measures in separate multiple regression analyses. Second-level models also included the regressors of no interest mentioned under subsection 'Analysis of BOLD response'. Second-level maps were thresholded voxelwise at $P < 0.001$ and corrected for multiple comparisons at a cluster threshold of $P < 0.05$ (family-wise error) for the whole brain. Clusters were considered

Table 2. Modulation of brain activity (BOLD response) and functional connectivity (PPI, source regions: left putamen and left amygdala) by BMI, craving intensity and Disinhibition

Brain region	*MNI peak coordinates*	*Peak z-value*	k	*P-value (FWE)*
Brain activity (BOLD response)				
BMI^2 (neg. correlation)				
REGULATE_TASTY > CRAVE_TASTY				
Left putamen	− 33, − 9, − 3	4.13	83	0.012
Left amygdala/hippocampus	− 30, − 3, − 18	3.86		
Left insula	− 39, − 12, 9	3.75		
Craving intensity (pos. correlation)				
CRAVE_TASTY > REGULATE_TASTY				
Right hippocampus/amygdala	30, − 18, − 15	4.45	107	0.004
	33, − 9, − 15	4.20		
Functional connectivity (PPI)				
BMI (pos. correlation), source region: left putamen				
REGULATE_TASTY > CRAVE_TASTY				
Left dlPFC	− 24, 33, 30	4.50	109	0.005
	− 33, 27, 24	4.09		
	− 33, 45, 30	3.92		
Left/right dmPFC/dlPFC	− 12, 21, 45	4.24	156	0.001
	9, 42, 45	3.83		
	− 15, 33, 48	3.79		
BMI^2 (pos. correlation), source region: left amygdala				
REGULATE_TASTY > CRAVE_TASTY				
Left pallidum	− 15, 0, 0	4.94	102	0.006
	− 21, 18, 3	3.64		
Left lingual gyrus	− 3, − 90, 6	4.62	121	0.003
	− 6, − 81, −9	3.62		
DIS (neg. correlation), source region: left amygdala				
REGULATE_TASTY > CRAVE_TASTY				
Right caudate (head)	9, 15, 3	4.23	63	0.040
	18, 18, 3	4.10		
Left/right dmPFC/dACC	0, 45, 27	4.13	78	0.019
	6, 54, 33	3.76		

Abbreviations: BOLD, blood-oxygen-level dependent; BMI, body mass index; dACC, dorsal anterior cingulate cortex; dlPFC, dorsolateral prefrontal cortex; DIS, disinhibition; dmPFC, dorsomedial prefrontal cortex; FWE, family-wise error; k, cluster size; MNI, Montreal Neurological Institute; neg., negative; pos., positive; PPI, psychophysiological interaction (correlations of Disinhibition are uncorrected for the number of investigated seeds). Results are thresholded voxelwise at $P < 0.001$ and corrected at a cluster threshold of $P < 0.05$ (FWE) for the whole brain.

to be significant at $P < 0.017$ (Bonferroni adjustment to account for the number of investigated seeds). Please see Supplementary Table III for a summary of performed regression analyses.

RESULTS

Relationships between BMI and eating behavior, craving intensity or subjective regulation success

We observed a strong positive correlation of BMI and DIS ($R^2 = 0.285$, $P > 0.001$, Pearson correlation, Supplementary Figure Ia). Multiple regression analysis revealed a negative association of BMI^2 with CR ($R^2 = 0.151$, $P = 0.038$, covariate BMI; Supplementary Figure Ib), indicating an inverted U-shaped relationship. Craving intensity did not correlate with BMI (R = − 0.206, $P = 0.185$, Pearson correlation). We found a trend of a negative correlation between regulation success and BMI (R = − 0.295, $P = 0.055$, Pearson correlation). See Table 1 for descriptive statistics.

Strategies

To regulate their craving, most of the participants (especially overweight volunteers) imagined the negative long-term consequences of eating the depicted palatable food. Most participants switched between different regulation strategies during the course of the experiment (see Supplementary Table IV for details on strategy use). When instructed to admit, all of the participants imagined taste or texture of the presented food items.

Relationships between BOLD activity and BMI, eating behavior, craving intensity or subjective regulation success

Activity in a cluster comprising left putamen, amygdala and insula was nonlinearly (inverted U-shaped) related to BMI during volitional regulation devoid of craving influences (REGULATE_TASTY > ADMIT_TASTY; Table 2, Figure 2). Activation during regulation specific to hedonic food (REGULATE_TASTY > REGULATE_NOT_TASTY) was unrelated to BMI. We found no linear relationships with BMI. Craving intensity correlated positively with activity in the right hippocampus/amygdala during craving devoid of volitional regulatory influences (ADMIT_TASTY > REGULATE_TASTY; Table 2, Supplementary Figure X), but did not correlate with activation during craving specific to hedonic food (ADMIT_TASTY > ADMIT_NOT_TASTY). Neither subjective regulation success nor measures of eating behavior were significantly related to task-related BOLD activity. The above-mentioned results indicate some lateralization of the findings. However, when a less strict threshold was applied, bilateral BOLD activation of all mentioned regions associated with BMI and craving intensity was observed (relationship of BOLD and BMI: t-values thresholded at $P < 0.05$, uncorrected; relationship of BOLD and craving intensity: t-values thresholded at $P < 0.001$, uncorrected).

Relationships between PPIs and BMI or eating behavior

The source regions for these analyses were based on areas whose BOLD activation was related to BMI, our primary target of interest. Therefore, seeds were defined as 4-mm spheres surrounding the peak voxels of the inverted U-shaped relationship between BMI and BOLD activation: putamen: − 33, − 9, − 3; amygdala: − 30, − 3, − 18; insula: − 39, − 12, 9 (REGULATE_TASTY > ADMIT_TASTY). Functional connectivity between the left putamen and the PFC (bilateral dlPFC extending into dmPFC) was positively and linearly associated with the BMI (Table 2; Figure 3a). Further, functional connectivity between the left amygdala and left pallidum (Table 2; Figure 3b, left/center) as well as the left lingual gyrus (Table 2; Figure 3b, right/center) was nonlinearly associated with BMI revealing U-shaped relationships. Considering eating behavior, DIS negatively correlated with functional connectivity between the left amygdala and contralateral caudate (Table 2; Figure 3c, left) as well as bilateral dmPFC including dACC (Table 2; Figure 3c, right). However, associations with DIS did not reach statistical significance after Bonferroni adjustment according to the number of the investigated seeds. Functional connectivity of the left insula was not associated with BMI or eating behavior. PPIs of all three source regions were not associated with CR. PPI results indicated some lateralization of the findings. However, applying a less strict threshold revealed bilateral connectivity changes of all reported regions associated with BMI and eating behavior (relationships with BMI: t-values thresholded at $P < 0.01$, uncorrected; relationships with DIS: t-values thresholded at $P < 0.001$, uncorrected). Please see Figure 4 for a simplified summary of the reported relationships.

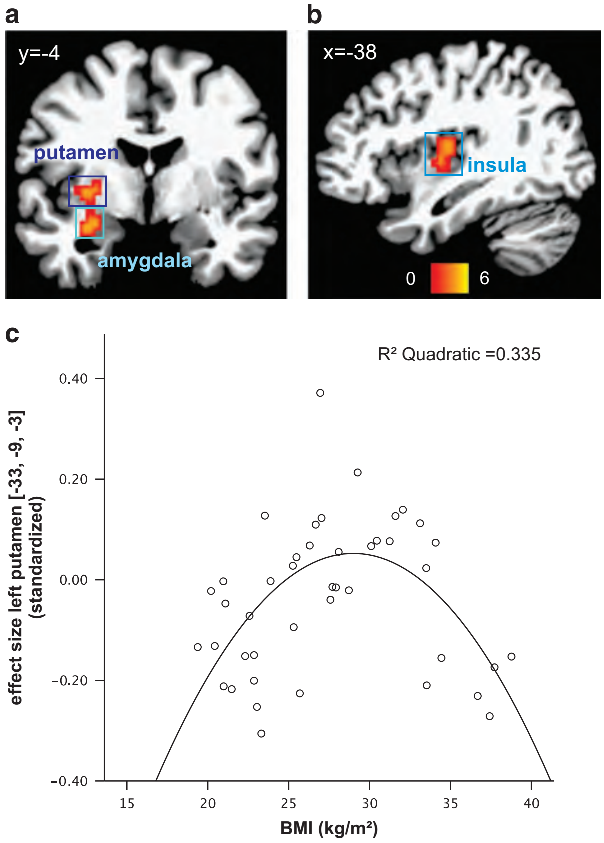

Figure 2. Modulatory effects of BMI on neural correlates of the volitional regulation of food craving (REGULATE_TASTY > CRAVE_TASTY). BMI is nonlinearly (inverted U-shaped) related to BOLD activation in a cluster of left (**a**) putamen, amygdala and (**b**) insula. (**c**) Inverted U-shaped relationship between BMI and BOLD effect size at the peak of this cluster in the left putamen. Color coding refers to t-values. Results are thresholded voxelwise at $P < 0.001$ and corrected at a cluster threshold of $P < 0.05$ (FWE) for the whole brain.

DISCUSSION

Brain mechanisms implicated in the regulation of food craving: relationships with weight status

Regulatory brain activity and BMI. Comparing regulation with craving revealed an inverted U-shaped relationship between BMI and activation in a cluster including left putamen, amygdala and insula; that is, a positive relationship in the range of normal weight and overweight (maximum in the range of mild obesity), which shifts to a negative one in the range of obesity. As these areas are known to mediate motivation related to food,[7,29–32] our findings supposedly indicate an effect of weight status on brain regulation of

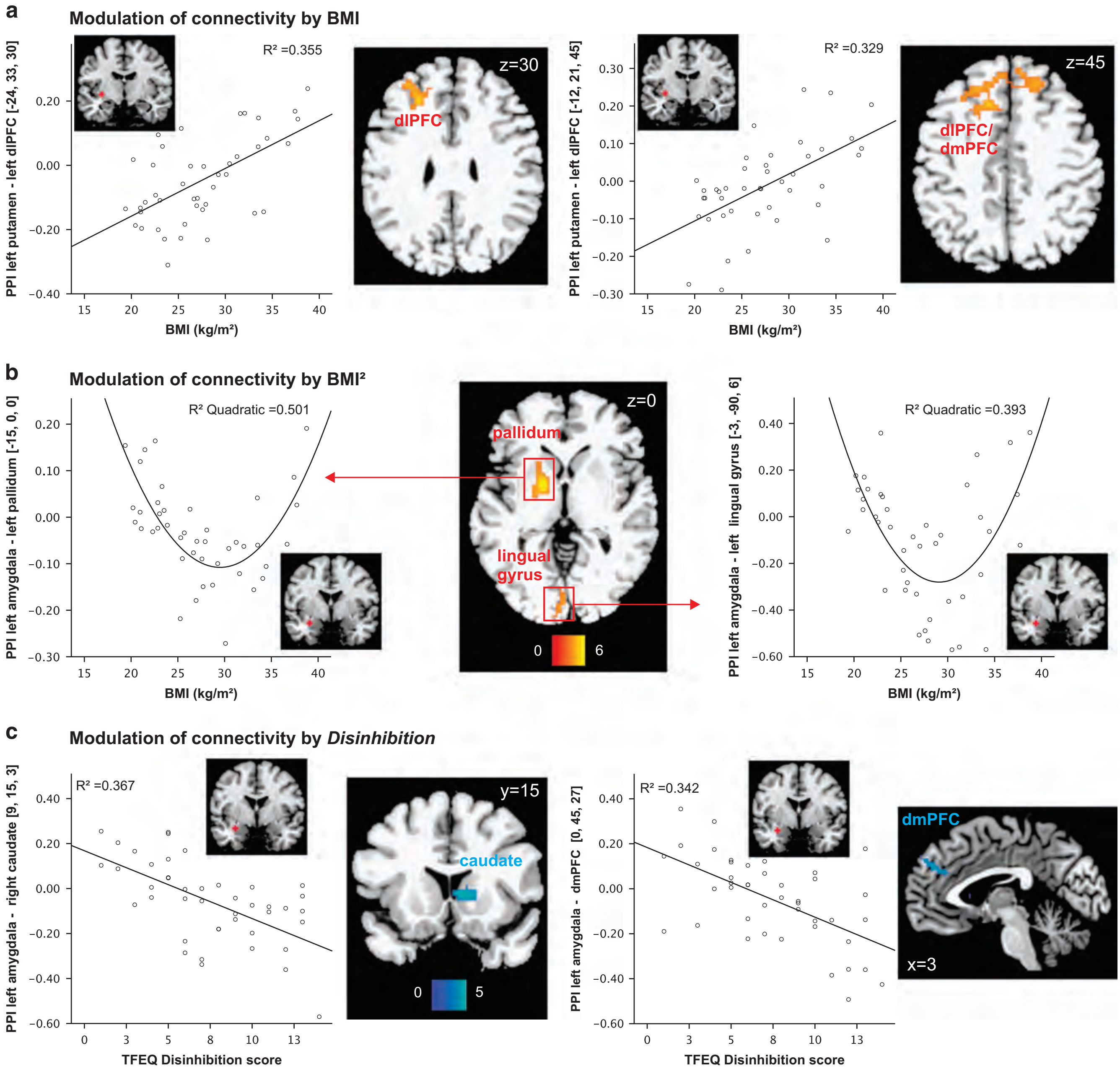

Figure 3. Modulatory effects of BMI and Disinhibition on functional connectivity (PPI) during the volitional regulation of food craving (REGULATE_TASTY > CRAVE_TASTY). Indicated are the respective relationships at the peaks of the detected clusters (scatter plots) as well as overlays of the clusters on a MNI brain template. The source regions (left putamen, left amygdala) are indicated as red overlays on a MNI brain template. (**a**) Positive linear association of BMI and functional connectivity (PPI) of left putamen with clusters in the PFC (left: cluster in left dlPFC, right: cluster in bilateral dlPFC/dmPFC). (**b**) U-shaped relationship of BMI and functional connectivity (PPI) of the left amygdala with the left pallidum (left, center) and the left lingual gyrus (right, center). (**c**) Disinhibition negatively scales with functional connectivity (PPI) of the left amygdala and the right caudate (left) as well as the left dmPFC (right). Color coding refers to *t*-values. The results are thresholded voxelwise at $P < 0.001$ and corrected at a cluster threshold of $P < 0.05$ (FWE) for the whole brain. The depicted relationships of Disinhibition are uncorrected for the number of investigated seeds. dlPFC, dorsolateral prefrontal cortex; dmPFC, dorsomedial prefrontal cortex; PPI, psychophysiological interaction; TFEQ, Three-Factor Eating Questionnaire.

food craving via modulation of motivational processing. We suggest the inverted U-shaped relationship to indicate enhanced motivational relevance of hedonic unhealthy food stimuli in the mid-BMI range in a context of volitional food-craving regulation. Differences in eating behavior may account for that. It was proposed previously that particularly overweight and mildly obese individuals are motivated to lose weight or avoid further weight gain, reflected in an inverted U-shaped association between BMI and dietary self-regulation.[20] These controlled eaters probably learned to associate the sight of desirable food with the negative consequences of their consumption. Enhanced activation of the putamen in the mid-BMI range might signal increased incentive drive towards avoidance of learned dieting cues since the putamen, as part of the basal-ganglia motivation-to-movement circuit,[33] was shown to be essential in instrumental performance[34] and has been assumed to be involved in potentiating learned dietary rules in successful dieters.[35] Further, results indicate that BMI-dependent differences in food-craving regulation may manifest on the level of the amygdala, a structure

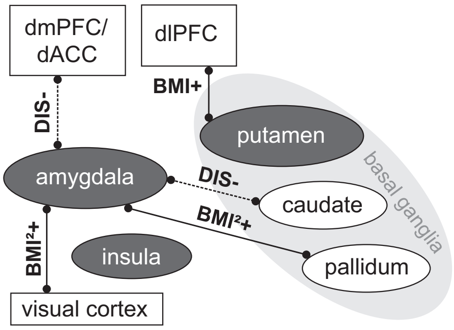

Figure 4. Brain mechanisms implicated in the volitional regulation of food craving and their interactions with weight status (BMI) and the individual tendency to overeat (DIS). Dark gray background: brain activity in these areas (putamen, amygdala, insula) has an inverted U-shaped relationship with BMI (that is, heightened response in overweight and mild obesity). White background: areas which are functionally connected to the putamen or amygdala, lines indicate the respective link and modulating factor: BMI+ indicates positive linear relationship with BMI, BMI^2+ indicates U-shaped relationship with BMI, DIS − indicates negative linear relationship with Disinhibition (dashed lines: underlying correlations are uncorrected for the number of investigated seeds). dACC, dorsal anterior cingulate cortex; dlPFC, dorsolateral prefrontal cortex; dmPFC, dorsomedial prefrontal cortex.

that encodes motivational salience of environmental stimuli such as food. In this way, the amygdala can trigger responses to arousing stimuli (for example, food)[8,30] and adjust the motivational level context-specifically (for example, regulation vs craving).[33] According to increased dietary restraint, palatable but unhealthy food stimuli might be particularly relevant in overweight or mildly obese individuals in the context of craving regulation, reflected in altered amygdala responding. Regulation-related left mid-insula processing was also nonlinearly associated with BMI. As the mid-insula integrates interoceptive visceral signals with information on salience or attention from anterior insula, weight status may further contribute to differences in craving regulation by modulating mid-insular affective mediation of autonomic activity.[36] This process may be enhanced in the mid-BMI range according to the suggested increased motivational salience or biological relevance of unhealthy palatable food cues.

Although the above-discussed interpretation of the association between BMI and BOLD activation is plausible, an alternative explanation for the detected inverted U-shaped relationship might exist. Volitional food-craving regulation may go along with counterproductive motivation regarding attractive food stimuli on the level of the brain. Increased eating-related self-control might enhance motivational brain mechanisms, inducing tendencies to approach palatable but unhealthy food especially in overweight/mildly obese individuals, as described previously for restrained eaters.[37]

Functional connectivity during regulation and BMI. During regulation, functional connectivity between the left amygdala and left pallidum as well as left lingual gyrus was nonlinearly (U-shaped) related to BMI. Therefore, weight status might affect the interplay between amygdala and pallidum,[38] a region implicated with food pleasantness signaling.[39] More specifically, BMI may affect craving regulation by a nonlinear modulation of the interaction between salience encoding (amygdala) and/or pleasantness computation (pallidum).[39] The lingual gyrus, on the other hand, plays a role in elementary processing of visual information.[40] Previous studies showed that emotional salience of a stimulus can influence such early stages of visual processing.[41] Therefore, weight-status-dependent variations in salience signaling (amygdala), as discussed above, might affect visual processing, presumably influencing subsequent perceptual experience or meaning of the presented stimuli as a means of BMI-dependent neural craving regulation. Importantly, the above-discussed interactions within the appetitive network supposedly vary especially between overweight and mildly obese individuals in comparison to normal-weight and more severely obese individuals, indicated by the U-shaped relationship.

Moreover, functional connectivity between the left putamen and the prefrontal cortex (dlPFC/dmPFC) was enhanced with higher BMI during regulation compared to craving. According to its role in coordinated context-specific goal-directed behavior,[42,43] the lateral prefrontal cortex supposedly integrates interoceptive hunger signals with external information on the food stimuli and internal rules about weight goals during craving regulation. The putamen, on the other hand, is presumably relevant to integrate this prefrontal information to modulate striatal incentive value representation and action selection.[33] The need for this prefrontal–striatal integration may be enhanced with a higher BMI, as indicated by the positive linear association. A reason for that may be working memory deficits with overweight and obesity,[44] that potentially complicate keeping the weaker but more favorable goal of food restriction (in contrast to food consumption) in an active state within working memory and appropriately adjust striatal value processing and action selection. Apart from that, increased top-down control of striatal value representation or action selection during craving regulation might be particularly necessary in individuals with a higher BMI to counteract enhanced sensitivity to food cues.[45]

Brain mechanisms implicated with the regulation of food craving: relationships with Disinhibition

Disinhibition scaled negatively with functional connectivity of left amygdala and left dmPFC including dACC during regulation compared to craving. This is in line with a previous study that showed reduced functional connectivity between the amygdala and dACC during the presentation of appetizing food in individuals with high external food sensitivity,[46] a trait that is reflected in the measure of Disinhibition. Neural activity within the dmPFC/dACC plays an important role in interpreting mental states[47] and conflict detection.[48] Further, medial prefrontal regions have been shown to project to the amygdala, which, in turn, sends outputs to autonomic brain centers.[38] Therefore, Disinhibition might affect neural craving regulation by influencing the prefrontal modulation of the affective response in the amygdala towards palatable but unhealthy stimuli. In highly disinhibited individuals, this may lead to an inappropriate affective response. Further, functional connectivity between caudate and amygdala was negatively associated with Disinhibition. The caudate receives and integrates value- and goal-related information to generate strategic action plans.[33] Therefore, decreased functional connectivity between the amygdala and caudate with higher Disinhibition might result in suboptimal modulation of striatal regulatory action planning by the context-specific salience signal of the amygdala. However, interpretations for Disinhibition should be regarded with some caution, as the underlying results are uncorrected for the number of investigated seeds.

Limitations and outlook

A strength of this study is the use of individually rated stimulus material. Nevertheless, we cannot exclude differences in the absolute subjective value depending on weight status. In addition, stimulus valence was assessed only explicitly. Implicit valuation might have additionally biased performance and brain activity. Further, findings are limited to the food-deprived status and might change considerably in a sated condition. In addition, this study is restricted to women. Future studies should include men as well. Moreover, Cognitive Restraint did not affect brain regulation of food craving, which is in line with other investigations,[13,35] but in contrast to our prior study.[16] However, the previous study mainly included normal-weight volunteers. Following up on this investigation, we now include an equally distributed number of normal-weight to obese participants. As Cognitive Restraint is related to BMI,[20] assessing the full BMI range increases variance of this measure, supposedly leading to an increased accuracy of the conducted analyses. Moreover, we instructed participants to apply everyday strategies but not specific ones. Thus, the effect of general regulatory brain activity was measured but not that of specific strategies. The participants approached the task in various ways. It seems reasonable that manifold strategy use translates into inter-individual variability in associated brain activity as shown in the context of emotion regulation.[49] Further, conclusions regarding successful dieting are complicated, as subjective regulation success did not correlate with activity in the above-mentioned regions. Underestimation of subjective regulation-related self-efficacy with higher BMI affecting performance rating might have contributed to this.[50] For future studies, we recommend post-experimental measurement of food intake to directly assess the regulation efficacy. Moreover, the ability to regulate food craving might be very different between everyday situations and an experimental setting. Nevertheless, a previous study indicated responsiveness of putamen and dorsal PFC to play a role in successful food restriction, as their activity was enhanced in successful dieters (determined by the Cognitive Restraint scale of the Three-Factor Eating Questionnaire[22]) after consumption of a meal.[35] Future studies should focus on longitudinal weight development to assess whether the detected relationships translate into successful weight control. Finally, we would like to stress the importance of replication studies, as the reported findings should be considered with some caution due to statistical thresholds less than the most conservative.

CONCLUSIONS

We showed for the first time nonlinear relationships between food-related brain processes and BMI, emphasizing the continuous nonlinear investigation of weight status and brain reactivity. Brain regulation of food craving in a food-deprived state seems to be reflected by an increase in motivational or incentive encoding of hedonic unhealthy food in the range of normal weight up to overweight/mild obesity and a decrease of this brain response in the range of obesity, supposedly related to previously learned associations of food stimuli and their negative consequences. The interplay between pleasantness signaling (pallidum) but also visual processing (lingual gyrus) and salience encoding (amygdala) seems to be nonlinearly affected by BMI, contributing to differences in neural craving regulation. The positive linear relationship of functional connectivity between the putamen and PFC may indicate a stronger need for top-down control of striatal value representation or action selection with higher BMI. Further, neural regulation of food craving might be hampered in highly disinhibited eaters as the interplay between salience signaling (amygdala) and prefrontal self-monitoring, as well as striatal eating-related strategic action planning may be affected in this individuals. Altogether, reported areas potentially represent targets for neurofeedback[51] interventions in the context of obesity. Overweight and obese subjects might be trained to control activity or connectivity within these areas or within striato-frontal networks by the help of feedback on the activity of these regions to induce changes in eating behavior. Therefore, our findings may help to develop new directions for obesity treatment.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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3 Summary

Zusammenfassung der Arbeit

Dissertation zur Erlangung des akademischen Grades Dr. rer. med.

Food craving regulation in the brain: the role of weight status and associated personality aspects

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3.1 English

Current obesity intervention programs typically show just small, short-lived changes in BMI (∼5%) [31–37] and many dieters regain weight after a diet [286, 287]. A reason for this lies in the difficulty to change unhealthy eating habits [38]. Therefore, a deep understanding of behavioral control mechanisms that help to avoid unhealthy eating behavior is needed to improve intervention programs and realize long-term weight loss. A main behavioral contributor to unhealthy eating and obesity is food craving - the intense desire for certain foods [1]. Cognitive behavioral approaches counteracting such strong food desires seem to be promising in the treatment of obesity [288]. However, to target food craving effectively, it is crucial to gain a profound understanding of the underlying biological mechanisms. In particular, it is necessary to understand brain mechanisms of craving regulation and how they are related to weight status or obesity-associated personality traits. Previous studies indicate food craving to be represented by a brain network processing food reward [16, 201, 289, 290]. Four interconnected structures form the core of this network: amygdala including hippocampus, striatum, ventromedial prefrontal cortex (vmPFC) including orbitofrontal cortex (OFC), and insula [16, 291]. During food craving regulation, responding of these areas is modulated by higher-order control regions (dorsal anterior cingulate cortex and lateral prefrontal cortex) [4–7, 196–198]. However, the relationship between neural correlates of food craving regulation and weight status is still an open issue. Existing imaging studies are inconsistent regarding associations of regulatory brain activity with the BMI [4–9]. The focus on normal-weight and obese samples with an underrepresentation of overweight individuals and the assumption of linear relationships might have contributed to this lack of knowledge. Strikingly, non-linear associations with BMI have not been investigated yet. However, there is indication for quadratic relationships, as U-shaped associations between BMI and behavior, particularly eating-related

self-control and reward sensitivity, have been found [258, 265]. Addressing this open issue, we investigated neural correlates, i.e., BOLD activity and functional connectivity as measured by functional magnetic resonance imaging (fMRI), of food craving regulation in a balanced sample of hungry normal-weight, overweight, and obese women. We aimed at identifying relationships with weight status (focusing on quadratic relationships) and obesity-associated aspects of human personality.

To specify personality traits of interest, we characterized relationships between BMI and obesity-relevant general and eating-specific personality characteristics and established a model for BMI based on these measures. The following personality measures, which are based on validated and well established self-report questionnaires, were considered for analysis: (a) characteristics of eating behavior based on the constructs of the *Three-Factor Eating Questionnaire (TFEQ)* [12, 292] including (1) *Cognitive Restraint*, (2) *Disinhibition*, and (3) *Susceptibility to Hunger* as well as (b) general aspects of personality including (1) sensitivity to reward and (2) sensitivity to punishment based on the *Behavioral Inhibition System/Behavioral Activation System (BIS/BAS) Scales* [10], and (3) impulsivity based on the *Barratt Impulsiveness Scale (BIS-11)* [11, 293]. Associations of BMI and the mentioned personality measures were explored in a sample of 326 (145 women; analyses on eating-related personality types only) or 192 (92 women; analyses including *BIS/BAS Scales* and *BIS-11*) healthy participants by the help of multiple regression analysis. Based on previous findings, quadratic relationships of BMI and *Cognitive Restraint* (moderated by *Disinhibition*) as well as BMI and sensitivity to reward (i.e., *BAS*) were tested.
We found an inverted U-shaped relationship between *Cognitive Restraint* and BMI which was moderated by the level of *Disinhibition*: For low *Disinhibition* scores the quadratic association of *Cognitive Restraint* with BMI was well pronounced, whereas no strong quadratic relationship was observed for high *Disinhibition* scores. We further found opposing relationships between BMI and sensitivity to reward (i.e., *BAS*) and sensitivity to punishment (i.e., *BIS*) in men (negative associations) compared to women (positive associations). Controlling for gender, an inverted U-shaped relationship between sensitivity to reward and BMI was observed. In the final regression model *Cognitive Restraint*, *Disinhibition* (considering their interaction) and sensitivity to reward/sensitivity to punishment (considering gender interactions) jointly explained 27% of the overall variance in weight status. *Susceptibility to Hunger* and self-reported impulsivity did not explain variance in BMI.
The inverted U-shaped relationship of *Cognitive Restraint* and BMI at low levels of *Disinhibition* indicates that food restriction may not be needed in normal-weight individuals and correspondingly *Cognitive Restraint* is low. With increasing BMI, food restriction presumably becomes relevant, resulting in increasing attempts to manage weight and higher *Cognitive Restraint* (reaching the maximum in the range of overweight/mild obe-

sity). Obese individuals, though, might not be able to raise sufficient self-control resources to restrict food intake [294–296], resulting in decreasing attempts to control weight in this BMI range and lower *Cognitive Restraint*. With higher levels of *Disinhibition*, eating behavior seems to be shaped towards more self-control in the normal-weight range of the BMI but dominance of uncontrolled eating in the overweight and obese range, as indicated by a less pronounced inverted U-shaped relationship. Moreover, the opposing relationships between sensitivity to reward and sensitivity to punishment and BMI in men and women might indicate gender differences in the reinforcing power of food [2, 297, 298] and the significance of emotional eating (to compensate punishments) [299, 300]; with women being more susceptible to these factors, potentially affecting weight status differently. According to our BMI model, five factors contribute to differences in weight status: (1) *Cognitive Restraint*, (2) *Disinhibition* (eating-specific factors); (3) sensitivity to reward and (4) sensitivity to punishment (general personality factors) as well as (5) gender. The relationship between impulsivity and weight status needs further investigation. As impulsivity is a multifaceted construct [246], some aspects of impulsivity may contribute to obesity while others do not. Behavioral intervention of overweight or obesity potentially benefit from our detailed specification of relationships between weight status and personality traits by individually adapting treatment based on personality characteristics and gender of the patient. Minimal effort is needed to implement the investigated questionnaires into a clinical setting ([301], publication 1).

In the fMRI part of this project we focused on weight status and the above specified personality types within the eating domain (*Cognitive Restraint, Disinhibition*). This investigation was an extension of the study of Hollmann et al. (2012) [5] mainly including normal-weight subjects. A balanced distribution of 43 normal-weight, overweight, and obese healthy women was now investigated (BMI: 19.4 – 38.8 $\geq$ 30 kg/m^2, mean 27.5 +/- 5.3 SD). Participants were presented with food pictures, individually pre-rated according to tastiness and healthiness, while scanned in a 3T whole-body MRI scanner. They were instructed to either admit to the upcoming craving for the presented food or to regulate it. By the help of regression analyses we analyzed relationships between regulatory brain activity (BOLD response) as well as functional connectivity and BMI or eating-related personality constructs (i.e., *Cognitive Restraint*, *Disinhibition*). Functional connectivity was assessed by means of psychophysiological interaction (PPI) analysis [302]. Source regions for PPI analysis were based on areas whose BOLD response was related to BMI (i.e., left putamen, amygdala, and insula).

During regulation, as compared to the craving phase, BMI was non-linearly (inverted U-shaped) related to brain activity in left putamen, amygdala, and insula. Functional connectivity of putamen and dorsolateral prefrontal cortex (dlPFC) was linearly associated with BMI, whereas connectivity of amygdala with pallidum and lingual gyrus was non-linearly (U-shaped) related to BMI. *Disinhibition* correlated negatively with changes in functional connectivity between amygdala and dorsomedial prefrontal (dmPFC) cortex as well as caudate.

This is the first study showing quadratic relationships between food-related brain processes and BMI, emphasizing the relevance of non-linear analyses in this context. The inverted U-shaped relationship between BMI and brain activity in putamen, amygdala, and insula indicates brain regulation of food craving to be reflected by differences in motivational signaling [184, 189, 303] regarding palatable but unhealthy food. It might increase in the range of normal weight up to overweight/mild obesity but decrease in the range of obesity. Differences in dietary restraint and accompanied variation in learned associations of food with the negative consequences of its consumption might account for the variation in brain responding [279, 304]. Connectivity analyses suggest that the need for top-down (dlPFC) adjustment [193, 305] of striatal value representations or action selection increases with BMI. The interplay between pleasantness signaling (pallidum [306]) but also visual processing (lingual gyrus [307]) and salience encoding (amygdala [183]) seems to be non-linearly affected by BMI, contributing to differences in neural craving regulation. *Disinhibition* might hamper the interplay between self-monitoring (dmPFC [191]) or eating-related strategic action planning (caudate [303]) and salience processing (amygdala). Further studies - especially longitudinal ones - are needed to clarify whether reported differences in brain regulation of food craving translate into effective weight management. Detected areas potentially represent targets for real-time fMRI neurofeedback training [13–15] which may be added to obesity interventions. By providing individuals with real-time information about brain activity in the detected regions or striato-frontal networks, overweight and obese individuals may learn to self-regulate this neural activity to more effectively change eating behavior. Therefore, our findings may help to develop new directions in obesity treatment ([308], publication 2).

3.2 German

Gegenwärtige Interventionsprogramme bei Adipositas haben meist nur geringe, kurzlebige Änderungen des BMI zur Folge (∼5%) [31–37], und erneute Gewichtszunahme nach einer Diät ist die Regel [286, 287]. Eine Ursache hierfür liegt in der Schwierigkeit, ungesunde Essgewohnheiten zu ändern [38]. Ein tiefgehendes Verständnis von behavioralen Kontrollmechanismen ist deshalb erforderlich, um Interventionsprogramme zu verbessern und langfristige Gewichtsreduktion zu realisieren. Einen Hauptanteil an ungesundem Essverhalten und Adipositas hat *Food Craving* - ein starkes Verlangen nach bestimmten Speisen [1]. Kognitive Verhaltensansätze, die diesem Verlangen entgegenwirken, scheinen vielversprechend für die Adipositasbehandlung [288]. Um jedoch dem *Food Craving* effektiv entgegenzuwirken, ist es wichtig, ein fundiertes Verständnis der biologischen Mechanismen dieses Prozesses zu erlangen. Insbesondere ist es notwendig, die zugrundeliegenden Hirnmechanismen der *Food Craving* Regulation und Zusammenhänge mit dem Gewichtsstatus und Adipositas-assoziierten Persönlichkeitsmerkmalen zu verstehen. Vorangegangene Studien deuten an, dass *Food Craving* durch ein Hirnnetzwerk abgebildet wird, welches bei der Prozessierung Essens-bezogener Belohnung von Bedeutung ist [16, 201, 289, 290]. Vier miteinander verknüpfte Regionen bilden das Herzstück dieses Netzwerks: Amygdala einschließlich Hippocampus, Striatum, ventromedialer Präfrontalkortex einschließlich Orbitofrontalkortex und Insula [16, 291]. Während der Regulation des *Food Cravings* wird die Aktivität dieser Regionen durch übergeordnete Hirnstrukturen (dorsaler anteriorer cingulärer Kortex, lateraler Präfrontalkortex) moduliert [4–7, 196–198]. Ungeklärt ist bisher jedoch, welche Assoziationen zwischen neuronalen Korrelaten des *Food Cravings* und dem Gewichtsstatus bestehen. Existierende bildgebende Untersuchungen sind inkonsistent hinsichtlich der Zusammenhänge zwischen regulatorischer Hirnaktivität und BMI [4–9]. Zu dieser Wissenslücke hat möglicherweise der Fokus auf normalgewichtige und adipöse Stichproben, wobei übergewichtige Personen vernachlässigt wurden, sowie die Annahme linearer Zusammenhänge beigetragen. Nicht-lineare Assoziationen wurden bisher nicht berücksichtigt, obwohl es Hinweise für quadratische Zusammenhänge gibt, die sich aus den U-förmigen Assoziationen zwischen BMI and Verhalten, speziell Selbstkontrolle und Belohnungssensitivität, ableiten [258, 265]. Um dieses Problem zu addressieren, untersuchten wir neuronale Korrelate - BOLD Aktivität und funktionelle Konnektivität erhoben mittels funktioneller Magnetresonanztomographie (fMRT) - der Regulation des *Food Cravings* in einer ausgewogenen Stichprobe hungriger normalgewichtiger, übergewichtiger und adipöser Frauen. Ziel war es, Zusammenhänge mit dem Gewichtsstatus (Fokus: quadratische Zusammenhänge) und Adipositas-assoziierten Persönlichkeitsmerkmalen zu identifizieren.

Zur Spezifizierung bedeutsamer Persönlichkeitsmerkmale wurden Beziehungen zwischen dem BMI und Adipositas-relevanten Persönlichkeitsmerkmalen charakterisiert und, basierend auf diesen Maßen, ein BMI-Modell etabliert. Folgende Persönlichkeitsdimensionen, beruhend auf validierten und gut etablierten Fragebögen zur Selbsteinschätzung, wurden für die Analysen herangezogen: (a) Maße des Essverhaltens - (1) *Kognitive Kontrolle des Essverhaltens/ gezügeltes Essen, (2) Störbarkeit des Essverhaltens* und (3) *Erlebte Hungergefühle* - basierend auf den Konstrukten des *Fragebogens zum Essverhalten* [12, 292]; sowie (b) allgemeine Persönlichkeitscharakteristika - (1) Sensitivität gegenüber Belohnungen und (2) Sensitivität gegenüber Bestrafungen basierend auf den Skalen des *Verhaltensaktivierungssystems* (*BAS*) und *Verhaltenshemmsystems* (*BIS*) [10] sowie (3) Impulsivität basierend auf der *Barratt Impulsivitäts-Skala* (*BIS-11*) [11, 293]. Assoziationen zwischen BMI und den aufgeführten Persönlichkeitsmaßen wurden in einer Stichprobe von 326 (145 Frauen, Analysen zu Maßen des Essverhaltens) bzw. 192 (92 Frauen, Analysen einschließlich *BIS/BAS Skalen* und *BIS-11*) gesunden Probanden mithilfe multipler Regressionsanalyse analysiert. Basierend auf vorhergehenden Befunden wurden quadratische Zusammenhänge zwischen BMI und der *Kognitiven Kontrolle des Essverhaltens* (Moderator: *Störbarkeit des Essverhaltens*) sowie BMI und Sensitivität gegenüber Belohnungen (*BAS*) getestet.

Wir konnten einen umgekehrt quadratischen Zusammenhang zwischen der *Kognitiven Kontrolle des Essverhaltens* und dem BMI nachweisen, der durch das Niveau der *Störbarkeit des Essverhaltens* moderiert wurde: Bei niedriger *Störbarkeit des Essverhaltens* war die Assoziation zwischen *Kognitiver Kontrolle des Essverhaltens* und BMI gut ausgeprägt, während kein starker quadratischer Zusammenhang bei hoher*Störbarkeit des Essverhaltens* beobachtet werden konnte. Außerdem wurden gegensätzliche Zusammenhänge zwischen BMI und der Sensitität gegenüber Belohnunegn (*BAS*) bzw. Sensitivität gegenüber Bestrafungen (*BIS*) bei Männern (negative Assoziationen) verglichen mit Frauen (positive Assoziationen) gefunden. Wurde für Geschlecht kontrolliert, zeigte sich ein umgekehrt quadratischer Zusammenhang zwischen der Sensitivität gegenüber Belohnungen und dem BMI. Das finale Regressionsmodell erklärt 27% der BMI-Varianz mittels der Prädiktoren *Kognitive Kontrolle des Essverhaltens*, *Störbarkeit des Essverhaltens* (einschließlich deren Interaktion) sowie Sensitivität gegenüber Belohnungen und Sensitivität gegenüber Bestrafungen (einschließlich Geschlechts-Interaktionen).

Der umgekehrt quadratische Zusammenhang zwischen *Kognitiver Kontrolle des Essverhaltens* and BMI bei niedriger *Störbarkeit des Essverhaltens* deutet an, dass Essenseinschränkungen bei Normalgewicht möglicherweise nicht notwendig sind und die *Kognitive Kontrolle des Essverhaltens* damit niedrig ist. Mit steigendem BMI ist anzunehmen, dass Maßnahmen der Essensrestriktion relevant werden und damit die *Kognitive Kontrolle des Essverhaltens* zunimmt (Maximum im Bereich Übergewicht/leichte Adipositas). Menschen mit Adipositas sind jedoch möglicherweise nicht in der Lage, genügend Ressourcen zur Selbstkontrolle des Essensverzehrs aufzubringen [294–296] und Anstrengungen zur Gewichtssteuerung und die *Kognitive Kontrolle des Essverhaltens* sinken. Angedeutet durch einen weniger stark ausgeprägten umgekehrt quadratischen Zusammenhang scheint bei höherer *Störbarkeit des Essverhaltens* das Essverhalten bei Normalgewicht von mehr Selbstkontrolle geprägt zu sein, wohingegen bei Übergewicht und Adipositas unkontrolliertes Essen zu dominieren scheint. Darüber hinaus deuten die gegensätzlichen Zusammenhänge zwischen der Sensitivität gegenüber Belohnungen und Sensitivität gegenüber Bestrafungen und dem BMI bei Männern und Frauen Geschlechtsunterschiede in der verstärkenden Wirkung von Essen [2, 297, 298] und der Bedeutung des Emotionsessens (zur Kompensation von Bestrafungen) an [299, 300]; wobei Frauen möglicherweise stärker empfänglich für diese Faktoren sind und der Gewichtsstatus damit anders beeinflusst wird. Unser BMI-Modell zeigte, dass fünf Faktoren zu Unterschieden im Gewichtsstatus der untersuchten Stichprobe beitrugen: (1) *Kognitive Kontrolle des Essverhaltens* und (2) *Störbarkeit des Essverhaltens* als essens-spezifische Faktoren, (3) Sensitivität gegenüber Belohungen und (4) Sensitivität gegenüber Bestrafungen als generelle Persönlichkeitsfaktoren, sowie (5) das Geschlecht. Der Zusammenhang zwischen Impulsivität und Gewichtsstatus bedarf weiterer Untersuchung. Da Impulsivität ein vielfältiges Konstrukt darstellt [246], tragen manche Aspekte möglicherweise zu Adipostas bei während andere keine Rolle spielen. Verhaltensinterventionen bei Übergewicht oder Adipositas können von der vorliegenden detaillierten Beschreibung der Zusammenhänge zwischen dem Gewichtsstatus und Persönlichkeitsmerkmalen profitieren, indem die Behandlung individuell - entsprechend von Persönlichkeitsausprägungen und des Geschlechts des Patienten - angepasst werden könnte. Minimaler Aufwand ist nötig, um die untersuchten Fragebögen im klinischen Rahmen zu implementieren ([301] Publikation 1).

Der Fokus der fMRT-Studie dieses Dissertationsprojektes lag - neben dem Gewichtsstatus an sich - auf den oben spezifizieren Persönlichkeitsmaßen des Essverhaltens (*Kognitive Kontrolle des Essverhaltens*, *Störbarkeit des Essverhaltens*). Diese Untersuchung war eine Erweiterung der Studie von Hollmann et al. (2012) [5], welche hauptsächlich normalgewichtige Probanden einbezog. Nun wurde eine ausgewogen verteilte Stichprobe von 43 gesunden normalgwichtigen, übergewichtigen und adipösen Frauen untersucht (BMI: 19.4 – 38.8 $\geq$ 30 kg/m^2, *M* 27.5 +/- 5.3 *SD*). Während 3T MR-Scans wurden den Probanden Essensbilder präsentiert, welche vorher individuell hinsichtlich Schmackhaftigkeit und Gesundheitsstatus bewertet wurden. Die Probanden wurden instruiert, ihr Verlangen nach diesen Speisen entweder zuzulassen oder zu regulieren. Mithilfe von Regressionsanalysen wurden Zusammenhänge zwischen regulatorischer Hinraktivität (BOLD-Antwort) sowie funktioneller Konnektivität und BMI bzw. Maßen des Essverhaltens (*Kognitive Kontrolle des Essverhaltens*, *Störbarkeit des Essverhaltens*) untersucht. Funktionelle Konnektivität wurde mittels PPI-Analyse (*psychophysiological interaction analysis*) ausgewertet [302]. Die Quellregionen der PPI-Analysen basierten auf Arealen, deren BOLD-Antwort mit dem BMI zusammenhing (linkes Putamen, linke Amygdala und Insula).

Während der Regulationsphase, im Vergleich zur Phase des Zulassens, zeigte sich ein nicht-linearer (umgekehrt quadratischer) Zusammenhang zwischen dem BMI und der Hirnaktivität des linken Putamens, der linken Amygdala sowie der linken Insula. Die funktionelle Konnektivität zwischen Putamen und dorsolateralem Präfrontalkortex hing linear mit dem BMI zusammen, wohingegen die der Amygdala mit Pallidum sowie Gyrus lingualis nicht-linear (quadratisch) mit dem BMI assoziiert war. Die *Störbarkeit des Essverhaltens* korrelierte negativ mit Änderungen der funktionellen Konnektivität von Amygdala und dorsomedialem Präfrontalkortex sowie Nucleus caudatus.
Dies ist die erste Studie, welche quadratische Zusammenhänge zwischen Essens-assoziierten Hirnprozessen und dem BMI demonstrieren konnte. Damit wird die Notwendigkeit von nicht-linearen Untersuchungen in diesem Kontext betont. Der umgekehrt quadratische Zusammenhang zwischen BMI und Hirnaktivität in Putamen, Amygdala und Insula deutet an, dass die Hirnregulation des Verlangens nach Essen im hungrigen Zustand durch eine Zunahme des motivationalen Signals [189, 303] bezüglich schmackhafter aber ungesunder Speisen im Bereich des Normalgewichts bis hin zum Übergewicht/ leichte Adipositas ansteigt, im Bereich der Adipositas jedoch wieder abnimmt. Verantwortlich dafür sind möglicherweise Unterschiede in der Kontrolle des Essverhaltens und damit verbundene Varianz in gelernten Assoziationen zwischen bestimmten Speisen und den negativen Konsequenzen des Verzehrs [279, 304]. Konnektivitätsanalysen deuten an, dass die Notwendigkeit einer übergeordneten Regulierung (dorsolateraler Präfrontalkortex [193, 305]) striatärer Wert-Repräsentationen oder Handlungsauswahl mit höherem BMI ansteigt. Das Zusammenspiel der Prozessierung von Schmackhaftigkeit (Pallidum [306]) sowie visueller Attribute (Gyrus lingualis [307]) und Salienz (Amygdala [183]) scheint nicht-linear mit dem BMI zusammenzuhängen, wodurch Unterschiede in der neuronalen Regulation des *Food Cravings* entstehen könnten. Die *Störbarkeit des Essverhaltens* beeinträchtigt andererseits unter Umständen das Wechselspiel zwischen Selbstbeobachtung (dorsomedialer Präfrontalkortex [191]) bzw. Essens-relatierter strategischer Handlungsplanung (Nucleus caudatus [303]) und Salienzprozessierung (Amygdala). Weitere Untersuchungen - vor allem Langzeitstudien - sind nötig, um zu klären, ob die berichteten Unterschiede hinsichtlich der Hirnregulation des *Food Cravings* effektiv zur Gewichtssteuerung beitragen. Die in dieser Studie gefundenen Regionen stellen potentiell Ziele für Echtzeit-fMRT Neurofeedback-Anwendungen dar [13–15], welche Adipositasinterventionen ergänzen könnten. Mittels Echtzeit-Information (Neurofeedback) über die Hirnaktivität in den berichteten Regionen oder striatär-frontalen Netzwerken könnten übergewichtige und adipöse Patienten lernen, diese Aktivierung selbstständig zu regulieren, um damit Änderungen im Essverhalten zu generieren. Erkenntnisse dieser Studie können damit dazu beitragen, neue Wege in der Adipositasbehandlung zu gehen ([308] Publikation 2).

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A Appendix

A.1 Supplemental material Dietrich et al., 2016

Brain regulation of food craving: relationships with weight status and eating behavior

Supplementary Material

Supplementary material provides details about relationships between BMI and characteristics of eating behavior measured by the *Three-Factor Eating Questionnaire*[1] (Figure Ia: BMI vs. *Disinhibition*, Figure Ib: BMI vs. *Cognitive Restraint*). It further includes task-related analyses of the BOLD response across all subjects (independent of BMI or eating behavior) (section II). The supplementary material provides information on the performed regression analyses (Table III) and strategy use during the regulation phase (Table IV). Moreover, it contains a graphical visualization of the relationship between brain activity and craving intensity (Figure X).

I Relationships between BMI and characteristics of eating behavior

A **B**

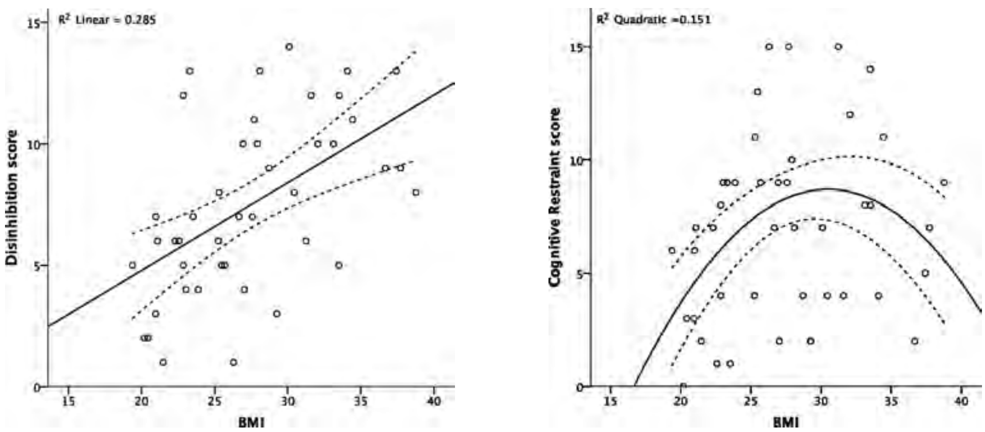

Figure I Relationships between BMI and characteristics of eating behavior. **(A)** Positive linear correlation between BMI and *Disinhibition*. **(B)** Inverted U-shaped relationship between BMI and *Cognitive Restraint*. Dashed lines indicate 95% confidence intervals.

II Task-related BOLD responses across all subjects (independent of BMI or eating behavior)

We designed a flexible factorial model including the factors ADMIT_TASTY, ADMIT_NOT_TASTY, REGULATE_TASTY, REGULATE_NOT_TASTY and a subject factor which accounts for interindividual variance. Contrasts were built to (1) identify regions that were more or less activated during REGULATION trials in contrast to ADMIT trials (main effects of REGULATION) and to (2) identify areas which were more or less activated during TASTY trials in contrast to NOT TASTY trials (main effects of TASTINESS). Further, the following REGULATION*TASTINESS interactions of interest were tested: ADMIT_TASTY > ADMIT_NOT_TASTY (i.e., craving response specific to hedonic food), ADMIT_TASTY > REGULATE_TASTY (i.e., craving response devoid of volitional regulatory influences), REGULATE_TASTY > REGULATE_NOT_TASTY (i.e., volitional regulation response specific to hedonic food), REGULATE_TASTY > ADMIT_TASTY (i.e., volitional regulation response devoid of craving influence). To assess, whether the above mentioned main effects were driven by a certain condition or stimulus type, the following interactions were tested as well: REGULATE_NOT_TASTY > ADMIT_NOT_TASTY, ADMIT_NOT_TASTY < REGULATE_NOT_TASTY. Table I gives an overview of performed tests.

Table I Tested main effects and interactions of BOLD activation across all subjects.

Main effects:
Main effects of regulation:
REGULATE_TASTY + REGULATE_NOT_TASTY > ADMIT_TASTY + ADMIT_NOT_TASTY
REGULATE_TASTY + REGULATE_NOT_TASTY < ADMIT_TASTY + ADMIT_NOT_TASTY
Main effects of tastiness:
ADMIT_TASTY + REGULATE_TASTY > ADMIT_NOT_TASTY + REGULATE_NOT_TASTY
ADMIT_TASTY + REGULATE_TASTY < ADMIT_NOT_TASTY + REGULATE_NOT_TASTY
Interactions of interest
REGULATE_TASTY > ADMIT_TASTY
REGULATE_NOT_TASTY > ADMIT_NOT_TASTY
ADMIT_TASTY > REGULATE_TASTY

ADMIT_NOT_TASTY > REGULATE_NOT_TASTY
ADMIT_TASTY > ADMIT_NOT_TASTY
REGULATE_TASTY > REGULATE_NOT_TASTY

REGULATION Analysis of the main effects of REGULATION revealed increased activation in frontal (bilateral IFG/ anterior insula, bilateral dmPFC, left dlPFC, right frontal pole), parietal (left inferior parietal lobule/ temporo-parietal-junction) and temporal (bilateral superior/ middle temporal gyrus) cortices and in cerebellum (Table II, Figure II). These effects were mainly driven by the BOLD response towards tasty cues, as the interaction REGULATE_TASTY > ADMIT_TASTY (regulation devoid of craving influences concerning tasty food) showed a comparable BOLD pattern, although partly left-lateralized (Table II, Figure V), whereas the contrast focusing on non-tasty food (REGULATE_NOT_TASTY > ADMIT_NOT_TASTY) revealed lower effect size BOLD activation in the same but much smaller prefrontal clusters and no parietal/temporal brain activation (Table II, Figure VI). Analysis of the main effects of REGULATION revealed decreased activation in bilateral vmPFC including left OFC, but also parietal cortical areas (bilateral postcentral gyri/left inferior parietal lobule, left parietal operculum), and left inferior temporal gyrus including fusiform gyrus (Table II, Figure III). These effects were primarily driven by tasty stimuli, as the interaction ADMIT_TASTY > REGULATE_TASTY (craving devoid of volitional regulation influences concerning tasty food) was characterized by a similar, though more extended activation pattern, including additionally limbic structures (left amygdala/ hippocampus), as well as occipital and midline cortical areas (left lateral occipital cortex/ precuneus/posterior cingulate cortex) (Table II, Figure VII), whereas the contrast focusing on non-tasty food (ADMIT_NOT_TASTY > REGULATE_NOT_TASTY) showed differences in the left postcentral gyrus only (Table II, Figure VIII).

TASTINESS Analysis of the main effects of TASTINESS revealed increased condition independent widespread activation in bilateral vmPFC, posterior cingulate cortices, dorsal striatum, and thalamus as well as in clusters of the medial temporal lobe (left fusiform/ parahippocampal gyrus), bilateral inferior temporal gyri, and cerebellum (Table II, Figure IV). These effects were driven by the ADMIT condition, as the contrast ADMIT_TASTY > ADMIT_NOT_TASTY (craving for tasty food) mostly reflects the above mentioned activation patterns (Table II, Figure IX). REGULATE trials did not add considerable variance to the main effects of tastiness, as their contrast (REGULATE_TASTY > REGULATE_NOT_TASTY) did not reveal significant differences. BOLD response was not decreased contrasting TASTY stimuli with NOT TASTY stimuli independent of condition (analysis of main effects of TASTINESS).

During craving and especially during craving for food with a high hedonic value participants showed increased activation of areas critical for subjective value computation (vmPFC, posterior cingulate),[2,3] eating-related incentive motivation and memory retrieval (hippocampal formation, amygdala, dorsal striatum),[4–7] as well as food-related sensory processing (postcentral gyrus, parietal operculum, fusiform gyrus, inferior temporal gyrus, lateral occipital cortex).[5,8,9] Importantly, only hedonic food stimuli activated regions that play a role in incentive value encoding (vmPFC, posterior cingulate, hippocampus, amygdala) or creation of incentive states (striatum),[10] emphasizing the usage of individually rated stimulus material in food-related tasks. The positive association of craving intensity and activation in hippocampus/ amygdala emphasizes their role in incentive value encoding.[6,7,32] During regulation (in comparison to craving), prefrontal areas associated with executive control (dlPFC, IFG, IPL)[2,11] as well as self-monitoring (dmPFC)[12] showed increased activation. These regions were especially activated during regulation of craving for hedonic food, as craving regulation is presumably more relevant in case of attractive unhealthy food. Nevertheless, also non-hedonic food activated executive control regions in this task. We assume that instructing participants to regulate their desire for food to some extent induced brain activity associated with, e.g., rule or strategy representation[11] regarding dietary restriction independent of hedonic value. The above mentioned results across all participants are in line with previous findings, proving conceptual validity of the study design.[13–19]

Table II Contrasts of experimental conditions across all subjects.

Brain region	**MNI peak coordinates**	**Peak z-value**	**k**
Main effects REGULATION			
REGULATE_TASTY + REGULATE_NOT_TASTY > ADMIT_TASTY + ADMIT_NOT_TASTY			
Left IFG (pars opercularis/pars triangularis)/ anterior insula	-54, 21, 3 -57, 21, 12 -45, 27, -6	7.26 6.63 6.56	503
Right IFG (pars opercularis/pars triangularis)/ anterior insula	42, 18, 3 57, 24, 9 30, 24, -9	6.39 5.89 5.65	512
Left/right dmPFC	-9, 57, 33 6, 18, 45 -6, 36, 51	5.44 5.09 5.06	545
Left dlPFC	-42, 3, 45 -48, 9, 45 -51, 18, 39	5.69 5.35 4.43	174

Right frontal pole	39, 39, 36 39, 48, 24 21, 60, 24	5.06 4.95 4.65	342
Left TPJ/IPL Left STG/MTG	-57, -54, 24 -48, -39, 3 -57, -36, 0	4.94 4.76 4.58	285
Right TPJ	57, -48, 30 63, -42, 18	4.55 3.48	103
Right STG/MTG	48, -30, -3 63, -30, -3	4.75 3.90	90
Right cerebellum	27, -81, -33 9, -84, -27	4.87 3.26	84
REGULATE_TASTY + REGULATE_NOT_TASTY < ADMIT_TASTY + ADMIT_NOT_TASTY			
Left postcentral gyrus Left IPL	-60, -18, 27 -48, -33, 42 -24, -42, 42	6.62 5.62 3.39	390
Left parietal operculum	-33, -6, 18 -27, -3, 24 -21, -3, 39	5.27 4.43 4.00	180
Right postcentral gyrus	66, -9, 30	5.20	62
Left OFC Left/right vmPFC	-21, 36, -12 -12, 42, -12 9, 30, -6	4.60 4.58 4.54	465
Left fusiform gyrus Left ITG	-36, -33, -15 -42, -45, -15 -51, -57, -6	4.27 4.13 3.73	113
Main effects TASTINESS			
ADMIT_TASTY + REGULATE_TASTY > ADMIT_NOT_TASTY + REGULATE_NOT_TASTY			
Left/right	-9, -51, 18	6.50	711

posterior cingulate cortex/ precuneus	-6, -54, 9 27, -57, 12	6.19 5.13	
Left/right vmPFC	-12, 45, -6 0, 42, -15 6, 51, -9	5.84 4.88 4.85	508
Left/right dorsal striatum Left thalamus	 -21, 6, 18 21, 15, 15 -21, -15, 18	 5.49 5.34 5.30	1552
Left lateral occipital cortex	-36, -75, 27 -33, -69, 12 -39, -66, 18	5.10 4.36 3.21	85
Left fusiform/parahippocampal gyrus Left ITG Left cerebellum	-24, -33, -24 -51, -48, -9 -18, -63, -36	4.40 4.19 4.17	265
Right ITG	57, -57, -12 42, -51, -6	4.37 3.49	56
ADMIT_TASTY + REGULATE_TASTY < ADMIT_NOT_TASTY + REGULATE_NOT_TASTY			
-	-	-	
Interactions			
REGULATE_TASTY > ADMIT_TASTY			
Left IFG (pars opercularis/pars triangularis)/ anterior insula	-51, 21, 3 -33, 11, -6 -48, 33, -9	6.20 6.07 5.57	450
Right IFG (pars opercularis/pars triangularis)/ anterior insula	42, 18, 3 33, 21, 0 39, 21, -6	6.57 6.26 6.13	992
Left/right dmPFC	-6, 36, 48 6, 18, 45	5.34 6.22	642

	9, 36, 51	4.85	
Left dlPFC	-48, 9, 45 -42, 3, 45 -42, 24, 33	5.36 5.29 3.86	164
Left TPJ/IPL	-57, -54, 27	4.82	51
Left STG/MTG	-48, -39, 3	4.06	62
REGULATE_NOT_TASTY > CRAVE_NOT_TASTY			
Left IFG (pars opercularis/pars triangularis)/ anterior insula	-42, 27, 0 -54, 21, 3 -57, 21, 15	5.22 5.15 4.82	245
Left dmPFC	-12, 57, 30 -6, 48, 36	4.56 3.83	63
Left dlPFC	-45, -3, 45 -36, 6, 45	4.16 3.23	65
Right IFG (pars opercularis/pars triangularis)/ anterior insula	48, 9, 0 54, 24, 3	4.02 3.75	65
ADMIT_TASTY > REGULATE_TASTY			
Left postcentral gyrus	-60, -18, 27 -48, -18, 24 -60, -12, 15	5.97 4.82 4.51	335
Left parietal operculum	-36, -6, 18 -24, 3, 24 -24, -12, 33	5.85 5.08 4.12	322
Left vmPFC Left OFC Right postcentral gyrus	-12, 42, -12 -24, 39, -9 66, -6, 27	5.43 4.58 4.96	860
Right ITG	48, -42, -12 39, -21, -18	4.91 4.04	83

Right fusiform gyrus	39, -30, -15	3.58	
Left fusiform gyrus Left ITG Left hippocampus/ amygdala	-36, -33, -15 -42, -45, -15 -30, -15, -15 -21, -3, -12	4.74 4.49 4.20	237
Left lateral occipital cortex Left precuneus, posterior cingulate cortex	-33, -66, 24 -36, -60, 3 -15, -51, 12	4.27 3.81 4.16	107
ADMIT_NOT_TASTY > REGULATE_NOT_TASTY			
Left postcentral gyrus	-60, -18, 30 -48, -36, 45	4.68 4.63	185
ADMIT_TASTY > ADMIT_NOT_TASTY			
Left/right posterior cingulate cortex vmPFC dorsal striatum	-9, -54, 18 -12, 42, -12 -21, -6, 21	6.65 5.27 4.69	2864
Left fusiform gyrus Left hippocampus Left parahippocampal gyrus	-24, -33, -24 -33, -27, -6 -36, -27, -18	5.16 5.10 4.23	226
Left MTG	-51, -12, -18 -60, -12, -12	4.74 4.38	59
Left cerebellum	-15, -57, -21	4.21	72
Right ITG	54, -51, -12	4.04	91
REGULATE_TASTY > REGULATE_NOT_TASTY			
-	-	-	-

Results are p<.05 FWE cluster-level corrected (voxel level p < .001); k = cluster size; dlPFC dorsolateral prefrontal Cortex, dmPFC dorsomedial prefrontal Cortex, IFG Inferior Frontal Gyrus, IPL Inferior Parietal Lobule, ITG Inferior Temporal Gyrus, MTG Middle Temporal Gyrus, TPJ Temporo-Parietal Junction, STG Superior Temporal Gyrus, vmPFC ventromedial prefrontal cortex

Main Effects

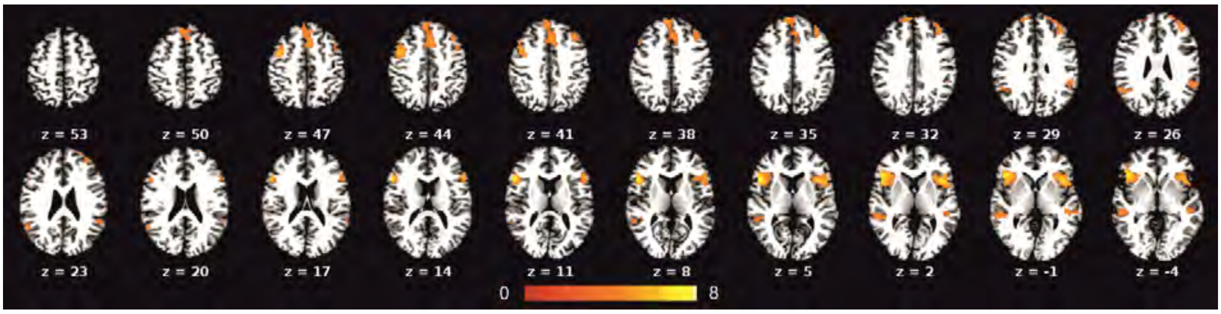

Figure II Main effects of REGULATION: REGULATE_TASTY + REGULATE_NOT_TASTY > ADMIT_TASTY + ADMIT_NOT_TASTY (threshold: p<.001 voxel level, p<.05 FWE cluster level).

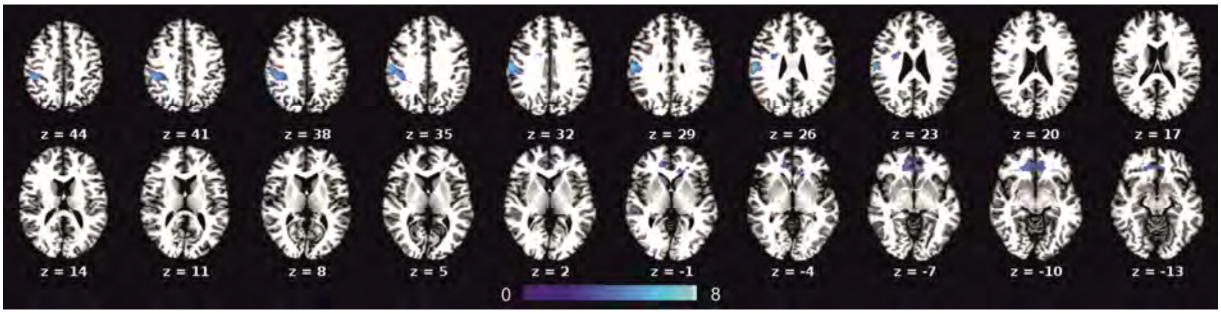

Figure III Main effects of REGULATION: REGULATE_TASTY + REGULATE_NOT_TASTY < ADMIT_TASTY + ADMIT_NOT_TASTY (threshold: p<.001 voxel level, p<.05 FWE cluster level).

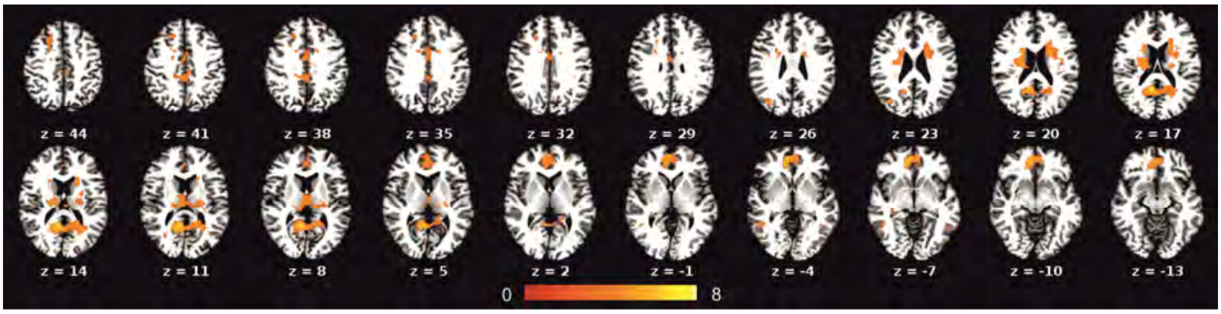

Figure IV Main effects of TASTINESS: ADMIT_TASTY + REGULATE_TASTY > ADMIT_NOT_TASTY + REGULATE_NOT_TASTY (threshold: p<.001 voxel level, p<.05 FWE cluster level).

Interactions

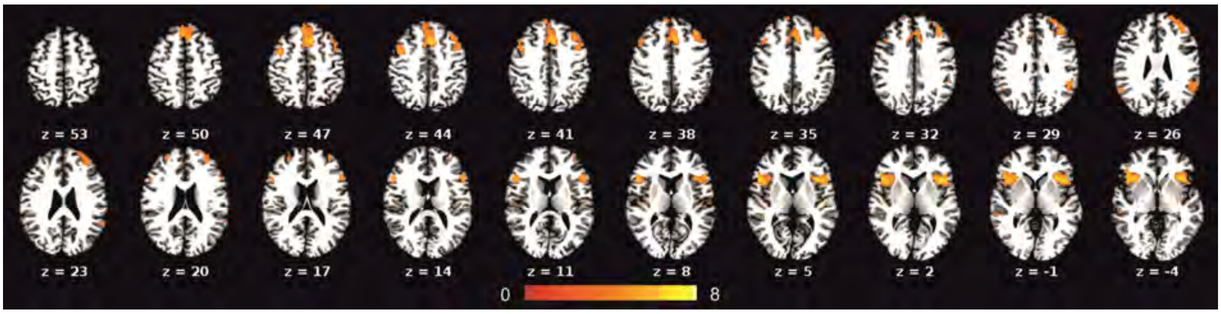

Figure V Interaction: REGULATE_TASTY > ADMIT_TASTY (threshold: p<.001 voxel level, p<.05 FWE cluster level).

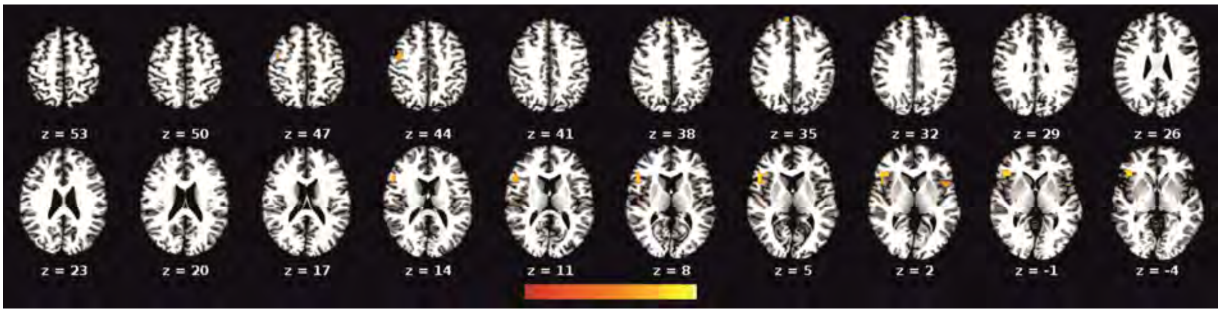

Figure VI Interaction: REGULATE_NOT_TASTY > ADMIT_NOT_TASTY (threshold: p<.001 voxel level, p<.05 FWE cluster level).

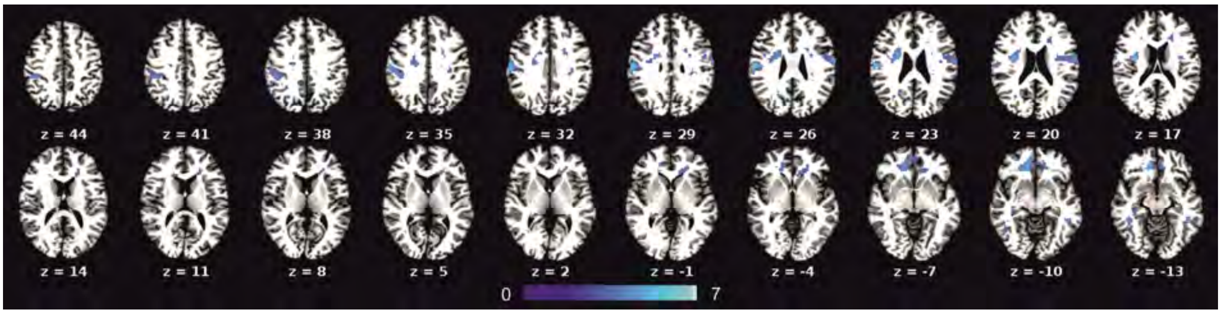

Figure VII Interaction: ADMIT_TASTY > REGULATE_TASTY (threshold: p<.001 voxel level, p<.05 FWE cluster level).

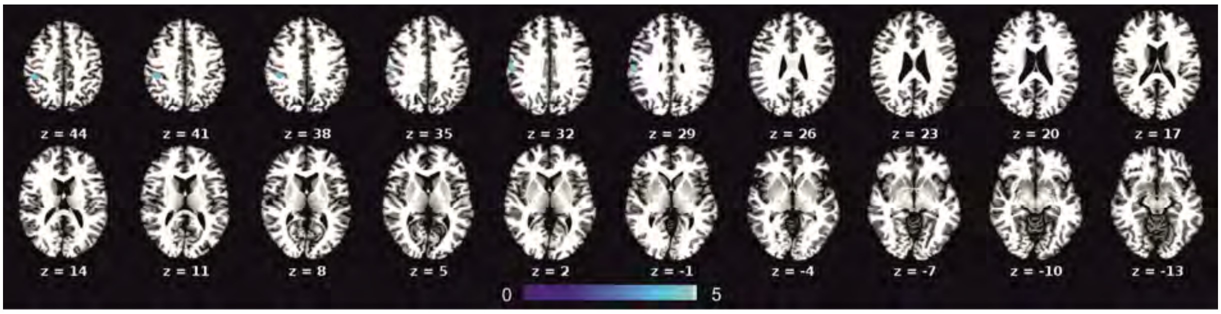

Figure VIII Interaction: ADMIT_NOT_TASTY > REGULATE_NOT_TASTY (threshold: p<.001 voxel level, p<.05 FWE cluster level).

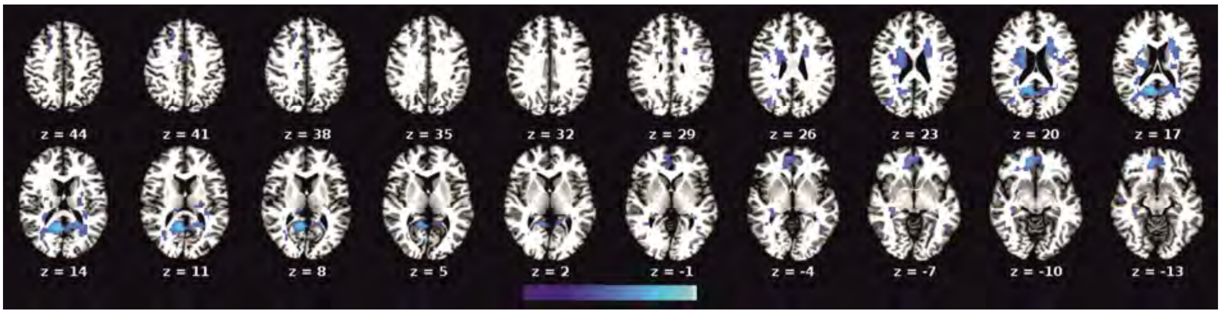

Figure IX Interaction: ADMIT _TASTY > ADMIT_NOT_TASTY (threshold: p<.001 voxel level, p<.05 FWE cluster level).

III Performed regression analyses

Table III Regression analyses of BOLD activation and psychophysiological interactions (PPI).

Regression analyses of BOLD response: ∑ = 12	
contrast	**regressors of interest**
REGULATE_TASTY > ADMIT_TASTY	BMI, BMI², CR, DIS, regulation success
REGULATE_TASTY > REGULATE_NOT_TASTY	BMI, BMI², CR, DIS, regulation success
ADMIT_TASTY > ADMIT_NOT_TASTY	craving intensity
ADMIT_TASTY > REGULATE_TASTY	craving intensity
Regression analyses of PPI: ∑ = 12	
contrast	**regressors of interest**
REGULATE_TASTY > ADMIT_TASTY	BMI, BMI², CR, DIS
(source regions: putamen, amygdala, insula)	

IV Strategy use during regulation

Table IV Applied regulation strategies. Indicated are the numbers of subjects (separated for normal weight, overweight, and obese participants) using a specific strategy. The application of several strategies was possible during the experiment.

Strategy	normal weight (n=15)	overweight (n=14)	obese (n=14)
imagination of long-term consequences of consumption	10	13	10
distraction	3	-	-
imagination of unappetizing ingredients, consistency, or preparation	2	2	5
other strategies	3	4	3

V Relationship between brain activity and craving intensity

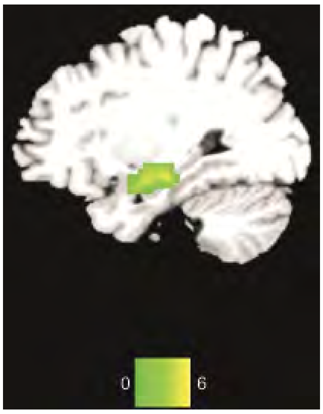

Figure X Relationship between activity in right hippocampus including amygdala and craving ratings during ADMIT_TASTY > ADMIT_NOT_TASTY. Threshold: $p<.001$ voxel level, $p<.05$ FWE cluster level.

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A.2 Declaration of authenticity

Erklärung über die eigenständige Abfassung der Arbeit

Hiermit erkläre ich, dass ich die vorliegende Arbeit selbständig und ohne unzulässige Hilfe oder Benutzung anderer als der angegebenen Hilfsmittel angefertigt habe. Ich versichere, dass Dritte von mir weder unmittelbar noch mittelbar geldwerte Leistungen für Arbeiten erhalten haben, die im Zusammenhang mit dem Inhalt der vorgelegten Dissertation stehen, und dass die vorgelegte Arbeit weder im Inland noch im Ausland in gleicher oder ähnlicher Form einer anderen Prüfungsbehörde zum Zweck einer Promotion oder eines anderen Prüfungsverfahrens vorgelegt wurde. Alles aus anderen Quellen und von anderen Personen übernommene Material, das in der Arbeit verwendet wurde oder auf das direkt Bezug genommen wird, wurde als solches kenntlich gemacht. Insbesondere wurden alle Personen genannt, die direkt an der Entstehung der vorliegenden Arbeit beteiligt waren.

Datum Unterschrift

A.3 Curriculum Vitae

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10/2009 - 03/2010	Tutor of practical training in animal physiology, Bachelor's program Biology, University of Leipzig

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07/2012 - 06/2015	Konrad-Adenauer-Stiftung

A.4 List of puplications

Dietrich A., de Wit, S., Horstmann, A. (2016). General Habit Propensity Relates to the Sensation Seeking Subdomain of Impulsivity But Not Obesity. Frontiers in Behavioral Neuroscience, 10: 213.

Dietrich A., Hollmann, M., Mathar, D., Villringer, A., Horstmann, A. (2016). Brain regulation of food craving: relationships with weight status and eating behavior. International Journal of Obesity, 40: 982–989.

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Dietrich, A., Federbusch, M., Grellmann, C., Villringer, A., Horstmann, A. (2014). Body weight status, eating behavior, sensitivity to reward/punishment, and gender: relationships and interdependencies. Frontiers in Psychology, 5: 1073.

A.5 Conference contributions

Dietrich, A., Hollmann, M., Mathar, M., Villringer, A., & Horstmann, A. (2015). Weight status and eating behavior affect how the brain regulates food craving. Poster presented at 1st Leipzig International Meeting for Interdisciplinary Obesity Research (LIMIOR), Leipzig, Germany.

Dietrich, A., Federbusch, M., Grellmann, C., Villringer, & A., Horstmann, A. (2014). Body weight status, eating behavior, sensitivity to reward/punishment, and gender: relationships and interdependencies. Poster presented at 30th Annual Meeting of the German Society for Obesity, Leipzig, Germany.

Dietrich, A., Hellrung, L., Hollmann, M., Pleger, B., Roggenhofer, E., Kalberlah, C., Villringer, A., & Horstmann, A. (2014). Intermittent compared to continuous real-time fMRI neurofeedback boosts control of amygdala activity. Poster presented at 20th Annual Meeting of the Organization for Human Brain Mapping (OHBM), Hamburg, Germany.

Dietrich, A., Hollmann, M., Villringer, A., & Horstmann, A. (2013). Functional differences in the volitional regulation of the desire for food between groups based on clustering of eating behavior and BMI. Poster presented at 29th Annual Meeting of the German Society for Obesity, Hannover, Germany.

Dietrich, A., Hollmann, M., Villringer, A., & Horstmann, A. (2013). Functional differences in the volitional regulation of the desire for food between groups based on clustering of eating behavior and BMI. Poster presented at Neuroeconomics: Decision Making and the Brain, Lausanne, Switzerland.

Horstmann, A., **Dietrich, A.**, Pleger, B., Villringer, A., & Hollmann, M. (2013). Clustering by weight and eating style reveals congruent structural and functional brain differences. Poster presented at 19th Annual Meeting of the Organization for Human Brain Mapping (OHBM), Seattle, WA, USA.

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