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Enhanced Neural Responsiveness to Reward Associated With Obesity in the Absence of Food-Related Stimuli

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Abstract: *Background:* Obesity has been characterized by alterations in brain structure and function associated with emotion processing and regulation. Particularly, aberrations in food-related reward processing have been frequently demonstrated in obese subjects. However, it remains unclear whether reward-associated functional aberrations in obesity are specific for food-related stimuli or represent a general deficit in reward processing, extending to other stimulus domains. Given the crucial role of rewarding effects in the development of obesity and the ongoing discussion on overlapping neurobiological traits of obesity and psychiatric disorders such as depression and substance-related disorders, this study aimed to investigate the possibility of altered reward processing in obese subjects to occur in the absence of food-related stimuli during a monetary reward condition. *Methods:* Twenty-nine healthy obese subjects (body mass index >30) and 29 healthy, age-, and sex-matched control subjects of normal weight underwent functional MRI during a frequently used card guessing paradigm. A Group × Condition (win vs. loss) ANOVA was conducted to investigate differences between obese and normal-weight subjects. *Results:* We found significant Group × Condition interaction effects in brain areas involved in emotion regulation and reward processing including the insula, the striatum, and the orbitofrontal cortex (OFC). This interaction was predominantly driven by a significant increase in blood oxygenation level dependent (BOLD) response in obese individuals while experiencing reward. *Conclusions:* Enhanced neural activation in obesity during reward processing seems to be

Additional Supporting Information may be found in the online version of this article.

Nils Opel and Ronny Redlich contributed equally to this work and should, therefore, both be regarded as first authors.

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apparent even in the absence of food-related stimuli and, thus, might point to generalized dysfunctions in reward-related brain circuits in obese individuals. *Hum Brain Mapp 36:2330–2337, 2015.*

Key words: obesity; body mass index; reward; MRI; fMRI

INTRODUCTION

Obesity represents an increasing health care problem in most industrial countries [World Health Organization, 2014]. Altered impulse control and reward processing are assumed to be among the decisive features in the development of adverse behavioral patterns in eating disorders [Bonato and Boland, 1983; García-García et al., 2014; Guerrieri et al., 2007]. Recent research provides evidence for the existence of neurobiological aberrations which might explain these behavioral characteristics in obese subjects [Batterink et al., 2010; Weygandt et al., 2013]. Particularly, the extending use of neuroimaging techniques successfully disclosed structural and functional traits of obesity in brain areas associated with emotion processing [Burger and Berner, 2014; Shott et al., 2014; Walther et al., 2010].

Recent structural imaging findings comprise decreased overall gray and white matter as well as specific alterations in prefrontal and striatal areas in obese individuals, brain structures which are closely linked to impulse control and emotion regulation [Opel et al., 2015; Raji et al., 2010]. Compared to structural imaging, functional studies benefit from the possibility of customized paradigms allowing insights into specific neural processing and, therefore, constitute an effective method in the elucidation of dysfunctional reward patterns underlying obesity [Blum et al., 2014; Bragulat et al., 2010; Burger and Stice, 2014; Dimitropoulos et al., 2012; Frank et al., 2012].

In fact, enhanced neural responsiveness to food-related reward constitutes one of the most consistent findings in functional magnetic resonance imaging (fMRI) studies on obesity [Burger and Berner, 2014; Dimitropoulos et al., 2012; Gearhardt et al., 2011].

Moreover, several studies using functional magnetic resonance imaging (fMRI) evidenced associations between food intake behavior and differences in reward processing: In a longitudinal study by Burger et al. [2014], future weight gain could be predicted by enhanced striatal responsivity during food-related reward learning and Batterink et al. [2010] found body mass index (BMI) scores to be negatively correlated with inhibitory control in response to food in obese individuals [Batterink et al., 2010; Burger and Stice, 2014].

However, as most fMRI studies in obesity used food or eating specific paradigms, the possibility of generalized dysfunctions in reward processing remains unclear.

The few studies available indicate that obesity might indeed be characterized by broader dysfunctions in emotion and reward processing [Balodis et al., 2013; Delgado-Rico et al., 2013].

In a study by Kishinevsky et al. [2012], executive function in the prefrontal cortex during a delay discounting trial could predict subsequent weight gain in obese subjects [Kishinevsky et al., 2012]. Moreover, Verdejo-Garcia et al. demonstrated associations between abnormal neural activation in reward brain regions and social decision-making in obese adolescents [Verdejo-García et al., 2014].

Regarding the ongoing discussion on overlapping neurobiological traits of obesity and psychopathological conditions, for example, substance-related disorders and affective disorders, it appears important to further examine the possibility of generalized reward deficiency in obesity [Blum et al., 2014; García-García et al., 2014].

Therefore, in this study, we investigated the possibility of altered reward processing in obesity in the absence of food-related reward stimuli. We suspected obese individuals to show increased neural responsiveness compared to normal-weight subjects during a monetary reward paradigm, particularly in prefrontal and striatal areas.

METHODS

Participants

Our study sample comprised 29 healthy obese subjects and 29 sex- and age-matched ($ps > 0.49$) healthy controls of normal weight. Due to excessive movements, two participants were excluded leaving a final study sample of 28 obese subjects (mean age = 43.8, SD = 8.9 years, mean BMI = 33.34, SD = 2.42) and 28 normal-weight subjects (mean age = 42.0, SD = 10.2 years, mean BMI = 22.64, SD = 1.44; see Table I). Inclusion criteria were defined as a BMI >30 for the obesity sample and a BMI of 20–25 for the normal-weight sample. For subjects of both samples, exclusion criteria were any history of neurological (e.g., concussion, stroke, tumor, neuroinflammatory diseases) and medical (e.g., cancer, chronic inflammatory or autoimmune diseases, heart diseases, diabetes mellitus, infections) conditions as well as regular intake of medication. All participants were free from any history of psychiatric disorders, according to the Structured Clinical Interview for DSM-IV (SCID) as conducted by a clinically experienced interviewer [Wittchen et al., 1997], had normal or corrected-to-normal vision, and had adequate knowledge of German and cognitive abilities (verbal IQ >80; multiple-choice vocabulary intelligence test MWT-B [Lehrl,

TABLE I. Sociodemographic characteristics of our final study sample consisting of 28 normal-weight healthy subjects and 28 obese healthy subjects

	Normal weight-sample ($n = 28$)			Obesity sample ($n = 28$)			
	Mean	SD	Range	Mean	SD	Range	*P*-value
Age	42.04	10.17	23–59	43.79	8.86	27–58	0.50
Sex (m/f)	15/13	NA	NA	15/13	NA	NA	1
BMI	22.64	1.44	20–25	33.34	2.42	30–40	<0.01
HAMD	0.89	2.01	0–8	0.68	1.36	0–6	0.64
BDI	1.96	2.22	0–7	1.18	1.36	0–5	0.12
Verbal IQ	118.36	12.82	95–143	114.93	13.26	94–136	0.33

Means, standard deviations (SD), and group differences (as measured with *t*-tests or χ^2-test).
Abbreviations: Beck Depression Inventory (BDI); Hamilton Depression Rating Scale (HAMD).

2005]). The Beck Depression Inventory (BDI) [Beck and Steer, 1987; Hautzinger et al., 1994] was used to assess the presence of depressive symptoms. Additionally, the 17-Item Hamilton Depression Rating Scale (HAMD) [Hamilton, 1960] was conducted by a clinical interviewer as an objective depressive severity measurement. Participants were recruited by public notices and newspaper announcements and received a financial compensation. The study was approved by the local Institutional Review Boards (IRB), and written informed consent was obtained from all participants before study participation.

Stimulus Materials and Procedure

We used a modified, frequently used card guessing paradigm [Delgado et al., 2005; Forbes et al., 2009] to detect brain activity associated with reward processing. All participants were told that the final amount of their monetary reward would depend on their performance on the card game and were, thus, unaware of the actually fixed outcome (10€).

The utilized pseudorandom block-design paradigm comprised nine blocks: three "win" blocks (block 1, 4, 7), three "lose" blocks (block 2, 5, 8), and three control blocks (block 3, 6, 9) with each block consisting of five trials. During each trial, subjects had 3 s to guess whether the value of a visually presented card was lower or higher than 5. After the choice was made, the numerical value of the card was presented for 0.5 s and followed by appropriate feedback (red down arrow for negative feedback, green up arrow for positive feedback) for an additional 0.5 s. Subjects were asked to confirm the gain via button press whenever positive feedback was given. Finally, a crosshair was presented for an alternating duration of 1.5 s for consecutive odd-numbered stimuli throughout the whole paradigm (i.e., for the first, third, fifth stimuli, etc.) or 2.5 s for consecutive even-numbered stimuli throughout the whole paradigm (i.e., for the second, fourth, sixth stimuli, etc.), resulting in a total trial length of 5.5 s and 6.5 s, respectively.

During the three "win" blocks, predominantly positive feedback (four trials, 80% correct) was given, whereas during the three "lose" blocks predominantly negative feedback (four trials, 80% false) was given. For each positive feedback, a fictional amount of 1€ was allocated while for each negative feedback a fictional amount of 50 Cents was discounted. The "win" and "lose" blocks were interleaved with three control blocks. During control blocks, subjects were requested to press a button at random during the presentation of an "x" (3 s), followed by an asterisk (0.5 s), a yellow circle (0.5 s), and a crosshair (again 1.5 s for odd-numbered stimuli; 2.5 s for even-numbered stimuli). All blocks were preceded by an instruction (3 s) resulting in a total block length of 32.5 s for odd-numbered blocks and 33.5 s for even-numbered blocks yielding a total task length of 296.5 s.

fMRI Data Acquisition and Analysis

T2* functional data were acquired using a 3 Tesla scanner (Gyroscan Intera 3T, Philips Medical Systems, Best, NL), using a single-shot echoplanar sequence, with parameters selected to minimize distortion in the region of central interest, while retaining adequate signal-to-noise ratio (S/N) and T2* sensitivity. Volumes consisting of 34 slices were acquired (matrix 64×64, resolution 3.6 mm × 3.6 mm × 3.6 mm; repetition time (TR) = 2.1 s, echo time (TE) = 30 ms, flip angle (FA) = 90°). The slices were tilted 25° from the anterior commissures/posterior commissures (AC/PC) line to minimize drop out artifacts in the mediotemporal and orbitofrontal region.

The paradigm presentation was projected to the rear end of the scanner (Sharp XG-PC10XE with additional high frequency (HF) shielding). During the experiment, subjects lay supine in the MRI scanner with the response box in their right hand. The head position was stabilized with a vacuum head cushion.

Data were analyzed using statistical parametric mapping software (SPM8, Welcome Department of Cognitive

Neurology, London, UK; http://www.fil.ion.ucl.ac.uk/spm). Preprocessing of our functional data included realignment, unwarping, and spatial normalization to MNI-space as well as smoothing with a Gaussian kernel of 6 mm full-width at half-maximum as described in our previous work [Donges et al., 2012].

To isolate neural response during the different blocks (control, win, lose), onsets and durations of the corresponding experimental conditions were modeled using a canonical hemodynamic response function. This was done in the context of the general linear model including corrections for serial correlations and application of a high-pass filter of 128 s to remove low-frequency noise.

For each subject, first-level analyses were conducted yielding two contrast-images "win > control" and "lose > control". One normal-weight subject and one obese subject had to be excluded due to excessive head movement (exclusion criterion >3 mm/3°).

Second-level analyses. To address our hypothesis of altered reward processing in obesity, we performed a 2 (group: obesity vs. normal-weight) × 2 (condition: reward > control vs. loss > control) ANOVA on whole-brain data, using a full factorial model, with group as between-subjects factor and reward condition as within-subjects factor. Post hoc *t*-tests were conducted to further investigate potential interaction effects. The anatomical labeling was performed by means of the AAL-Toolbox [Tzourio-Mazoyer et al., 2002], and the Brodmann areas (BA) were identified with the Talairach Daemon atlas (http://www.talairach.org).

To control for multiple statistical testing, we maintained a cluster-level false-positive detection rate at $P < 0.05$ using a voxel-level threshold of $P < 0.001$ with a cluster extent (k) empirically determined by Monte Carlo simulations ($n = 5{,}000$ iterations). This was performed by means of the AlphaSim [Forman et al., 1995] procedure, implemented in the REST toolbox (http://restfmri.net/forum/index.php) as reported in our previous publications [Dannlowski et al., 2014, in press; Opel et al., 2014]. The empirically determined cluster threshold for whole-brain data was $k = 101$ voxels.

RESULTS

The Group × Condition ANOVA revealed significant interaction effects in the orbitofrontal cortex (OFC) extending to the insula and the putamen ($x = -26$, $y = 22$, $z = -10$; $F_{(1,108)} = 22.26$; $P < 0.001$; $k = 132$ voxels), as well as in areas of the prefrontal cortex including the middle frontal gyrus, the superior and the inferior frontal gyrus ($x = -26$, $y = 40$, $z = 16$; $F_{(1,108)} = 18.28$; $P < 0.001$; $k = 169$ voxels).

Post hoc analysis yielded a significant increase in BOLD contrast in obese subjects compared to normal-weight subjects for the reward versus control condition in clusters again including the insula extending to the OFC and the putamen (right: $x = 36$, $y = 18$, $z = -14$; $t_{(108)} = 5.18$; $P < 0.001$; $k = 208$ voxels, left: $x = -28$, $y = 24$, $z = -8$; $t_{(108)} = 5.09$; $P < 0.001$; $k = 206$ voxels) and prefrontal areas including the middle frontal gyrus ($x = -36$, $y = 32$, $z = 24$; $t_{(108)} = 4.39$; $P < 0.001$; $k = 355$ voxels, $x = -28$, $y = 60$, $z = 6$; $t_{(108)} = 4.27$; $P < 0.001$; $k = 400$ voxels). Furthermore, significant enhancement in BOLD response for the reward versus control condition in the obese group could be detected in the anterior cingulate cortex ($x = 6$, $y = 42$, $z = 6$; $t_{(108)} = 4.23$; $P < 0.001$; $k = 101$ voxels) and several temporal, occipital, and cerebellar brain areas (cuneus/precuneus: $x = 12$, $y = -80$, $z = 24$; $t_{(108)} = 4.56$; $P < 0.001$; $k = 736$ voxels, angular gyrus: $x = 50$, $y = -70$, $z = 28$; $t_{(108)} = 4.92$; $P < 0.001$; $k = 178$ voxels, cerebellum: $x = 34$, $y = -72$, $z = -32$; $t_{(108)} = 4.42$; $P < 0.001$; $k = 167$ voxels; see Figure 1, Table II).

No significant increase in BOLD contrast could be found in normal-weight subjects compared to obese subjects regarding the reward versus control condition and no significant differences between both groups regarding the loss versus control condition could be detected at the applied thresholds ($P < 0.001$, $k > 101$).

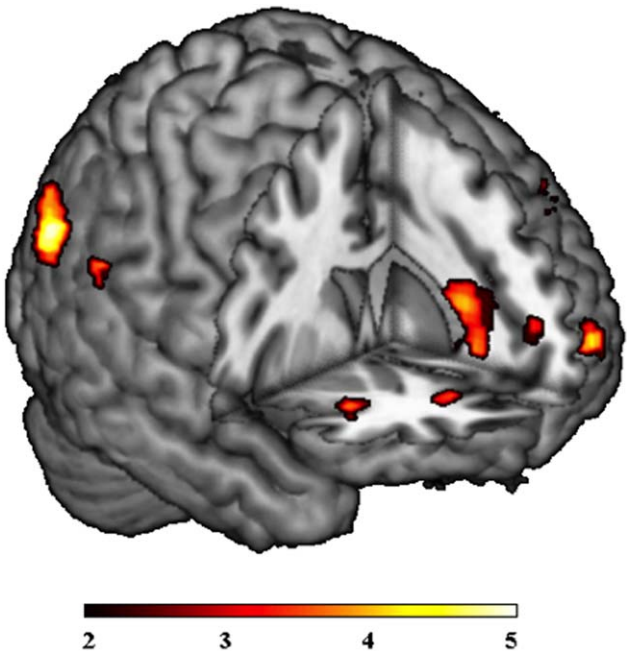

Figure 1.
Obesity is associated with enhanced neural responsiveness to reward. Rendered brain surface (cutout at MNI coordinates at x = −14, y = 6, z = -5) depicts the results of a t-test contrasting both groups (Obesity > Normal Weight) for the reward > control condition showing the ACC, and the OFC. Color bar: Tvalue. Abbreviations: MNI, Montreal Neurological Institute, ACC, Anterior Cingulate Gyrus, OFC, Orbitofrontal Cortex. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

TABLE II. Results of the post hoc t-tests displaying clusters with significantly enhanced neural responsiveness to reward (versus control) in obese subjects compared to normal-weight subjects[a]

	BA	Cluster size (k)	MNI (at peak) x	y	z	Side	T-value
Insula/Inferior Frontal Gyrus, orbital part/Putamen	47/13/45	208	36	18	−14	R	5.18
Insula/Inferior Frontal Gyrus, orbital part/Putamen	47/13	206	−28	24	−8	L	5.09
Angular Gyrus/Middle Occipital Gyrus/Middle Temporal Gyrus	39/19	178	50	−70	28	R	4.92
Cuneus/Precuneus/Calcarine Gyrus/Superior Occipital Gyrus/Middle Occipital Gyrus	31/19/7/ 18/30/23	736	12	−80	24	R	4.56
Cerebellum	—	167	34	−72	−32	R	4.42
Middle Frontal Gyrus/Inferior Frontal Gyrus Pars Triangularis	9/46/10/45	355	−36	32	24	L	4.39
Middle Frontal Gyrus/Superior Frontal Gyrus	10/32/24/8	400	−28	60	6	L	4.27
Anterior Cingulate Gyrus/Middle Frontal Gyrus, orbital part	32/24	101	6	42	6	R	4.23
Inferior Parietal Gyrus/Angular Gyurs	40	103	−38	−56	34	L	4.07

Abbreviations: MNI, Montreal Neurologic Institute.
[a]All reported whole-brain analyses were conducted with a voxel-threshold of $P < 0.001$, minimum cluster volume threshold $k \geq 101$. Coordinates based on MNI atlas.

In a second step, to rule out a potential contribution of frequently observed structural alterations in obese subjects, mean gray matter values of each subject were added to the model as nuisance regressor using Voxel-Based-Morphometry as described in our previous work [Dannlowski et al., in press; Opel et al., 2014; Redlich et al., 2014a, b] (see Supporting Information). However, the inclusion of structural data as a covariate did not change the pattern of our results (see Supporting Information Table I).

Additionally, we conducted a psychophysiological interaction analysis (PPI) to detect possible patterns of altered network connectivity related to the reward versus control condition as used by Laeger et al. [Friston et al., 1997; Laeger et al., 2014]. Therefore, the cluster demonstrating the strongest effect in the preceding fMRI post hoc t-test (reward > control contrast for obese > normal-weight subjects) was defined as seed region ($x = 36$, $y = 18$, $z = -14$, $k = 208$ voxels). The signal time course of this seed was extracted and the reward > control contrast served as psychological factor. The individual contrast images of the PPI term reflecting the influence of task condition on network connectivity were compared between obese and non-obese subjects. Yet, no significant differences between both groups could be found regarding the functional coupling at the applied thresholds ($P < 0.001$, $k > 101$).

DISCUSSION

With this study, we provide evidence for frequently observed alterations in reward processing to emerge independently from food-related stimuli in obesity. As suspected, obese individuals exhibited enhanced neural activation in areas assumed to be involved in reward processing during a common monetary reward paradigm. Our results suggest that adverse patterns of neural processing during reward experiences in obesity are apparent beyond the subject area food and, thus, might point to generalized dysfunctions in reward processing in obese individuals.

Obese subjects showed increased BOLD response to reward (but not loss) in the OFC, the striatum, the insula, and the anterior cingulate cortex compared to subjects of normal weight. This observation of enhanced neural response toward rewarding stimuli in prefrontal and subcortical areas matches results from previous neuroimaging studies on obesity using food-stimuli [Burger and Berner, 2014; Dimitropoulos et al., 2012; Gearhardt et al., 2011].

The critical role of medial prefrontal, insular, and striatal areas in obesity also finds support in results of previous fMRI studies reporting altered neural activation during impulse control and decision-making to predominantly emerge in similar brain areas [Batterink et al., 2010; Delgado-Rico et al., 2013]. Furthermore, the apparent consensus on the importance of aberrations in reward-specific brain areas like the OFC, the striatum, and the cingulate cortex in the development of obesity leans on findings from structural neuroimaging research [Bolzenius et al., 2015; Marqués-Iturria et al., 2013; Opel et al., 2015; Raji et al., 2010]. This suggests that both structural and functional aberrations might be present and could simultaneously contribute to the etiological processes underlying obesity. Interestingly, the results of this study might, however, implicate that structural and functional alterations do not mutually depend on each other, as we found that inclusion of structural data did not affect the pattern of our functional results. Rather, it seems that obesity might be

associated with different specific morphological and functional changes. Moreover, studies on resting state function in obesity indicated that functional alterations could possibly exceed the domain of neural reward processing [García-García et al., 2013; Kullmann et al., 2012; Zhang et al., 2015]. Furthermore, functional connectivity analyses revealed an excessive modulation of the ventral striatum by the orbitofrontal cortex during food reward processing in obese subjects [Carnell et al., 2012; Stoeckel et al., 2009]. It has been suggested that these altered connections in obese subjects might lead to enhanced food-craving in response to food cues [Stoeckel et al., 2009]. However, our finding of enhanced neural activation in obese subjects during reward in the striatum, the insula, and the OFC does not seem to substantially arise from aberrant network connectivity, as no significant PPI could be detected.

There has been growing evidence on the adverse clinical effects of abnormal neural processing in areas closely linked to the reward system in obesity, inter alia future weight gain [Batterink et al., 2010; Kishinevsky et al., 2012].

As altered reward processing seems to appear in a most common situation-like monetary gain in obese subjects, one might conclude that the neural alterations underlying this trait could also bear adverse effects in varying circumstances.

Among others, a shared neurobiological background of obesity and substance addiction has been frequently discussed and supports this hypothesis [García-García et al., 2014]. Also, Tomasi et al. (2014) previously demonstrated overlapping patterns of neural response in the OFC to cocaine as well as to food cues and points to the critical role of the dopaminergic system in both food and drug addiction [Tomasi et al., 2014], and furthermore, genetic variation in the dopaminergic system was reported to alter striatal responsiveness to reward [Dannlowski et al., 2013; Forbes et al., 2009]. Indeed, dysfunctions in dopamine pathways have been suggested to interfere in the development of severe obesity, affective disorders, and substance addiction and might, therefore, constitute an essential link between these conditions [Blum et al., 2014; Opel et al., 2015; Wang et al., 2009].

This notion is supported by recent findings regarding the importance of the dopamine system in obesity: First, D2 receptor availability has been shown to be significantly decreased in obese subjects and second, decreased striatal D2 receptor availability has been demonstrated to be positively correlated with prefrontal metabolism [Volkow et al., 2008; Wang et al., 2001].

Consequently, our findings of prefrontal and striatal hyper-reactivity might actually reflect blunted reward responsiveness in obesity as proposed by Carnell et al. [2012]. Given the decisive role of reward deficiency in addictive and affective disorders, our results shed more light on possible neurobiologial underpinnings underlying the high prevalent comorbidity of obesity and psychiatric disorders [De Wit et al., 2010].

As a basic function of reward is to induce a subjective feeling of pleasure and positive emotion, altered responsiveness to reward and, thus, reinforcing stimuli might contribute to the generation and maintenance of depressive symptoms, which could reflect the higher prevalence of depression in obese participants compared to normal-weight participants [Carey et al., 2014; Luppino et al., 2010].

The key role of reward-related brain areas like the OFC and the cingulate cortex in both affective disorders and obesity combined with findings of directly overlapping gray matter reductions in these particular areas in obesity and major depression highlight the possibility of a shared neurobiological background underlying this high prevalent comorbidity [Drevets, 2007; Opel et al., 2015].

Our observation of generalized dysfunctions in reward-related brain circuits in obesity, thus, underlines the importance of further investigation of possible clinical and neurobiological overlaps between obesity and further psychopathological conditions. In particular longitudinal studies should aim to investigate bidirectional associations between obesity and highly prevalent psychopathologic disorders, both sharing prefrontal and striatal alterations referring to a common key factor in the development of these disorders: the reward system.

Strengths of our study include the solid sample size. All of our participants were free from severe comorbidities including diabetes and cardiovascular disease which are high prevalent in obese subjects and might, therefore, constitute a confounding factor. Moreover, we used a robust paradigm which has frequently been shown to provide reliable results in studies on reward processing [Delgado et al., 2005; Forbes et al., 2009].

Some limitations must be acknowledged. First and foremost, we did not perform neuropsychological testing and, thus, could not provide information on impulsivity or behavioral control nor did we assess information on state of satiation in our subjects. We further did not control for potential confounding effects of smoking and alcohol intake, albeit substance abuse or addiction was an exclusion criterion. Studies investigating reward valence revealed that particularly medial OFC (MOFC) activation is associated with positive reward and with its subjective feeling of pleasantness [Kringelbach, 2003; Kringelbach and Radcliffe, 2005; Liu et al., 2011; Walter et al., 2008]. Due to the lack of data on subjective evaluation we cannot provide information about a potential association of functional activation patterns and the subjective feeling of pleasantness in this study. Furthermore, as our study design is cross-sectional, no statement on causal relationships can be made and, therefore, our interpretation of the data must be treated with care.

CONCLUSION

To conclude, enhanced neural activation in obesity during reward processing seems to be apparent in the absence of food-related stimuli and, therefore, might point to broader dysfunctions in reward-related brain circuits in

obese individuals. This finding of a generalized reward deficiency in obesity might highlight the importance to further explore possible shared neurobiological traits in obesity and psychopathological conditions which could lead to a better understanding and potentially advanced treatment options in obesity.

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