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ORIGINAL ARTICLE

Increased dorsolateral prefrontal cortex activation in obese children during observation of food stimuli

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Objective: Food cues yield different patterns of brain activation in obese compared with normal-weight adults in prefrontal and limbic/paralimbic areas. For children, no mapping studies comparing representation sites for food and other stimuli between obese and normal-weight subjects are available.
Design: We used a cross-sectional design of two age-matched subject groups to investigate differences in brain activation in response to visually presented food, pleasant, and neutral pictures between obese/overweight and normal children.
Subjects: 22 overweight/obese children were compared with 22 normal-weight children.
Measurements: Functional magnetic resonance imaging (of the whole head during perception of visually presented stimuli), psychological testing, and psychophysical measures of heart rate deceleration were assessed.
Results: Obese children showed higher activation of the dorsolateral prefrontal cortex (DLPFC) in response to food pictures. In addition, DLPFC activation was negatively correlated with self-esteem. In contrast, normal-weight children showed higher activation of the caudate and hippocampus specific to food pictures, and of the anterior cingulate cortex and thalamus to visual cues in general. In response to food stimuli, obese children showed a heart rate deceleration correlating positively with activation of the ventrolateral prefrontal cortex.
Conclusion: Obese children react to food stimuli with increased prefrontal activation, which might be associated with increased inhibitory control.
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Keywords: children; emotional processing; functional imaging; inhibitory control

Introduction

Food stimuli show comparable increase of functional activation in areas, which are part of the brain reward circuitry, as neuropharmacologic drugs.[1,2] This brain reward circuitry is a fundamental mechanism of appetite and food intake regulation.[3–5] Dopamine influences food intake by evaluating environmental cues and modulating food reward through the mesolimbic dopaminergic system and its projections to the hypothalamus and the amygdala,[6–8] leading to appetite, food seeking, and consumption.[5] Research on addiction and obesity has linked lower dopamine D2 receptor density, or D2 receptor dysfunction, to a higher vulnerability to substance abuse and excessive food intake.[9–11] As a kind of self-healing process, 'reward deficiency syndrome' leads individuals to consume high amounts of substances, such as alcohol, drugs, or food, which cause a release of dopamine in the dopaminergic reward system.[12]

It is intriguing to speculate that there exists a brain region that might help overcome temptations. Particularly for obese people, food cues are highly salient stimuli. However, they also entail a great conflict potential, as they know that they gain weight by consuming them. The prefrontal cortex (PFC) could well be such an area, as it is involved in cognitive behavior, monitoring inhibitory control, self-regulation and self-control.[13–17] Over dense interconnections between the PFC and basal ganglia through fronto-subcortical circuits,[18] the PFC exerts its top–down control, integrates external sensory and internal state information, leading to goal-directed behavior and inhibition of inappropriate response tendencies.[19–21] The functional organization of the PFC is

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somewhat understood: orbital and medial areas are thought to be related to behavioral inhibition, whereas ventrolateral and dorsal regions should be associated with memory or attentional functions.[22,23] The ventral part of the PFC is often summerized as the orbitofrontal cortex (OFC). However, the precise spatial differentiation of this area is inconsistent. We may divide the OFC into two subdivisions: the ventromedial PFC (VMPFC), more involved in stimulus driven processing of emotional materials, and the ventrolateral PFC (VLPFC), involved in more cognitive aspects of emotional material.[16]

Functional neuroimaging studies on human appetite and food intake regulation promote the existence of a central 'orexigenic network' and of a prefrontal 'satiation domain', inhibiting the activity in orexigenic areas.[24,25] These studies have concentrated on changes in brain activity during states of hunger and satiation in healthy individuals in response to food cues. Areas of the central 'orexigenic network', consisting of the hypothalamus, the thalamus, limbic/paralimbic areas (VLPFC and VMPFC, insular cortex, anterior cingulate cortex (ACC), amygdala), and basal ganglia (caudate, putamen), show an increase in activity during hunger and a decrease during satiation.[24–29] In contrast, the 'satiation domain', sited in prefrontal areas,[25] exhibits an increase in activity during satiation,[29] which has especially been shown in the VMPFC[25,28] and the dorsolateral PFC (DLPFC).[28]

Neuroimaging research on obesity has revealed differential patterns of neural activity in obese versus lean individuals in the orexigenic and satiation networks. These differences include a greater deactivation of limbic/paralimbic areas[28–30] and areas of the dopaminergic system,[24] less deactivation of the hypothalamus,[28,31] and a greater activation of prefrontal areas[28,29] in response to satiation. Others showed that obese people when observing food stimuli show even higher activations in areas associated with reward—quite comparable to patients suffering from addictive disease.[32] All these changes in blood oxygen level dependency (BOLD) response to observation of food stimuli have been only described in adult subjects, but no comparable data for children are available.

Only two neuroimaging studies have investigated the processing of food cues in children and adolescents. Holsen *et al*.[33] found increased activation in the amygdala, limbic/paralimbic regions (middle frontal/orbitofrontal cortex, insula, parahippocampal, and cingulate gyrus) and the fusiform gyrus, while viewing pictures of food during a state of hunger, compared with healthy adult subjects. Moreover, Killgore and Yurgelun-Todd[34] found greater activation of the hippocampus and cingulate cortex during viewing of high versus low caloric food cues, as well as age-related changes in neural activity within the OFC and the ACC. In conclusion, no study up yet has investigated the fMRI response of overweight children in comparison to normal-weight children on food stimuli.

This study investigated whether brain responses to food cues were different in overweight and obese versus normal-weight children and adolescents. On the basis of the earlier findings in adults, we hypothesized that there would be different patterns of brain activity during viewing of food pictures in limbic/paralimbic areas, especially the PFC, ACC, insula, hippocampus and amygdala, basal ganglia (caudate, putamen), and diencephalic regions (thalamus, hypothalamus) in obese versus normal-weight children. According to the reward deficiency syndrome, we predicted differences in activation of reward-related areas in normal weight versus obese children during viewing of food cues. Furthermore, we hypothesized a higher activation of regions of the orexigenic network during the food condition in lean subjects. Finally, we predicted a greater inhibitory control, thus greater PFC activity in obese versus normal weight in response to food stimuli. This has repeatedly been linked to a higher risk for obesity. To investigate whether the differences in brain responses were indeed specific to the processing of food and did not generalize to other appetitive stimuli, we used both emotionally neutral pictures and other pleasant but non-food-related pictures as controls.

Materials and methods

Participants

Sixty-two overweight and obese children and adolescents were recruited in the pediatric clinic by newspaper announcements, as well as by general practitioners, pediatricians, school doctors, and youth welfare offices who were all informed about a weight-loss-program at the pediatric clinic of the University of Greifswald. Only those children with a BMI–standard deviation score over 1.5 resembling a BMI of 22.5[35] were included for the patient group (see Table 1 for demographic data of patients and controls). Exclusion criteria were a history of psychiatric disease such as personality disorders or depression, eating disorders (bulimia, anoxeria), and oligophrenia.

Eleven overweight and obese children were not able to complete the fMRI scan because of anxiety or claustrophobia. Fifteen scans had to be excluded because of excessive motion artifacts (cutoff: 2 mm per 2° in any direction) preventing accurate measurement.

Thirty-six normal-weight controls without any history of neurological or psychiatric disease were recruited by announcement at the pediatric clinic, sports clubs, and local newspapers. Owing to braces, anxiety, or claustrophobia, seven scans could not be finished. Seven scans had to be excluded because of excessive motion artifacts (cutoff: 2 mm per 2° in any direction). The remaining 22 normal-weight subjects (mean age: 13.54 years, s.d. = 2.90, range: 9.56–18.30 years; 10 males; mean BMI: 19.70; s.d. = 2.50; mean percentile: 55.90; s.d. = 24.03; BMI–SDS: 0.16; s.d. = 0.79, range: −1.77–1.39) and 22 overweight and obese subjects, who were matched for age (mean age: 13.49 years, s.d. = 2.30, range: 9.57–17.60 years; 7 males; mean

Table 1 Demographic data of subject groups

Subject	*Class*[a]	*Sex*	*Age (years)*	*Size (m)*	*Weight (kg)*	*BMI (kg m^{-2})*[b]	*Percentile*[c]	*BMI–SDS*
Overweight and obese								
1	ov	F	11.05	1.53	52.6	22.47	93.34	1.50
2	ov	F	11.05	1.46	48.3	22.97	93.63	1.61
3	ob	F	11.73	1.57	82.7	33.55	99.88	3.03
4	ov	F	11.91	1.45	51.3	24.40	95.81	1.73
5	ob	F	12.88	1.60	86.1	33.63	99.83	2.93
6	ob	F	13.24	1.76	92.4	29.83	99.29	2.45
7	ob	F	13.68	1.72	86.5	29.24	98.94	2.31
8	ob	F	14.01	1.66	77.7	28.20	98.12	2.08
9	ob	F	14.23	1.63	81.2	30.94	99.34	2.48
10	ov	F	14.99	1.74	80.2	26.49	95.63	1.71
11	ob	F	15.21	1.53	70.6	30.16	98.83	2.27
12	ob	F	15.49	1.68	104.9	37.17	99.90	3.09
13	ob	F	16.21	1.73	106.8	35.68	99.91	3.12
14	ov	F	17.09	1.64	73.4	27.29	96.08	1.76
15	ov	F	17.60	1.86	93.4	27.00	95.15	1.66
16	ob	M	9.57	1.48	70.9	32.37	99.93	3.20
17	ob	M	10.46	1.49	56.3	25.70	98.65	2.21
18	ob	M	11.11	1.53	74.6	31.87	99.60	2.65
19	ob	M	11.63	1.46	53.9	25.29	97.10	1.90
20	ob	M	12.24	1.61	82.5	31.83	99.53	2.60
21	ob	M	15.19	1.77	94.0	30.00	98.96	2.31
22	ob	M	16.24	1.72	93.6	31.64	99.31	2.46
Subject	*Sex*	*Age (years)*	*Size (m)*	*Weight (kg)*	*BMI (kg m^{-2})*	*BMI-percentile*	*BMI–SDS*	
Normal weight								
1	F	9.56	1.44	33.1	15.96	35.95	−0.36	
2	F	9.61	1.38	33.1	17.38	61.72	0.30	
3	F	9.87	1.50	48.0	21.33	91.72	1.39	
4	F	11.79	1.59	45.3	17.92	45.68	−0.11	
5	F	12.59	1.60	54.0	21.09	79.97	0.84	
6	F	12.98	1.54	42.2	17.79	32.12	−0.46	
7	F	14.28	1.65	59.4	21.82	79.14	0.81	
8	F	15.00	1.66	59.2	21.48	66.19	0.42	
9	F	15.26	1.59	61.0	24.13	87.23	1.14	
10	F	16.22	1.74	61.4	20.28	51.36	0.03	
11	F	17.24	1.78	61.1	19.28	23.23	−0.73	
12	F	18.30	1.68	62.2	22.04	62.68	0.32	
13	M	12.72	1.70	58.0	20.07	69.27	0.50	
14	M	9.82	1.38	32.1	16.86	49.38	−0.02	
15	M	10.37	1.43	32.2	15.75	28.25	−0.58	
16	M	11.09	1.67	55.8	20.01	81.07	0.88	
17	M	12.02	1.54	40.8	17.20	37.00	−0.33	
18	M	12.22	1.64	50.4	18.74	61.08	0.281	
19	M	16.14	1.80	70.2	21.67	66.11	0.42	
20	M	16.32	1.66	69.2	25.11	91.19	1.35	
21	M	16.40	1.84	56.9	16.81	3.85	−1.77	
22	M	18.11	1.77	65.1	20.78	25.52	−0.69	

[a]Classification: ov, overweight; ob, obese. [b]BMI calculated in accordance to the Centers for Disease Control (CDC) guidelines. [c]Percentile of the BMI in respect to the age-matched distribution.

BMI: 29.44 +3.87; mean percentile: 98.03; s.d. = 2.07; mean BMI–standard deviation score: 2.32, s.d. = 0.54, range: 1.50–3.20) were included in the final analysis (see Table 1). Of the patient group, six subjects were overweight; the others were obese (CDCS classification). To avoid complicated phrasing, we further indicate the patients group as 'obese'. All subjects had normal or corrected-to-normal vision. The study was approved by the Ethics Committee of the Medical Faculty of the University of Greifswald. The parents of all participants provided written informed consent.

Stimulus materials and procedure

In both subject groups, seven children were measured in a time window of 2 h after meal, the other 15 were measured in a time window with >2 h from the last meal. Therefore,

the time of the last food intake was roughly balanced between subject groups. During the fMRI experiment, participants viewed full color photographs selected from the International Affective Picture System (Center for Psychophysiological Study of Emotion and Attention).[36] The pictures were derived from the following three categories: food (pizza, hamburger, sweets; average arousal: 6.03 (scale from 1 to 9); average valence: 5.35 (scale from 1 to 9), pleasant (young animals, babies, children playing; average arousal: 6.42; average valence: 5.55), and neutral (landscapes, buildings, work-related situations; average arousal: 5.49; average valence: 6.34). There were 20 photographs in each category. During scanning, stimuli were presented in alternating blocks lasting 30 s. Each block contained 20 pictures of the same category, with a total of five blocks of each category presented in random order. Each image was shown for 1500 ms, with the order randomized within each block, minimizing the effect of habituation. During the 15-s inter-block-intervals, the screen was black. The beginning of a new block was initialized with a red fixation cross that was presented for 1500 ms.

Stimuli were projected onto a translucent screen and were viewed by participants through a mirror attached to the head coil. The mirror was adjusted before the session to ensure an optimal view. Before scanning, participants were told not to move during the entire session, to keep their eyes open, and to watch the pictures attentively, even if some of the pictures might be unpleasant to them. After the scanning session, the pictures were presented again outside the scanner. Participants rated their experienced pleasure and arousal immediately after viewing each of the pictures using the nine-point Self-Assessment Manikin-Scale.[37]

Apparatus and data acquisition

fMRI data. MRI was conducted on a 1.5 T scanner (Siemens Magnetom Symphony, Erlangen, Germany) equipped with an eight-channel headcoil. Field homogeneity was optimized before each session by using a shimming sequence. Subsequently, a T1-weighted anatomical volume (TR: 368 ms, TE: 4.88 ms, flip angle: 40°, FoV: 192 mm, matrix: 256×256, voxel size: $1 \times 1 \times 1$ mm) was recorded. Although presenting the picture blocks, 225 volumes with 33 slices each (3–mm thick, 0.75–mm gap) were acquired in transversal direction parallel to the AC-PC line. Functional imaging was performed using echo-planar images (TR: 3000 ms, TE: 50 ms, flip angle: 90°, FoV: 192 mm, matrix: 64×64, voxel size: $3 \times 3 \times 3$ mm).

Psychological testing and physiological recordings. Assessing their perceived self-esteem and self-competence, all participants had to complete the FSK-K questionnaire (a German questionnaire constructed to assess self-esteem and perceived self-competence).[38] In a different session outside the scanner, an electrocardiogram (Eindhoven Lead II) was recorded using two Hellige AG/AgCl standard electrodes (8 mm diameter), whereas the participants were viewing the same pictures as in the scanner. R-waves were defined using a custom-made heart rate trigger (modified according to Shimizu[39]). The analog signal was continuously sampled at a rate of 1000 Hz.

Data analysis

fMRI data. Preprocessing and statistical analysis was performed using the Statistical Parametric Mapping software (SPM5; http://www.fil.ion.ucl.ac.uk./spm) running on Matlab (Version 7.4; MathWorks Inc., Natick, MA, USA). The first two functional volumes were discarded, accounting for signal equilibration. Preprocessing included reslicing, spatial realignment, and unwarping in phase encoding direction, normalization into the MNI space, as well as spatial (FWHM 12 mm) and temporal high (cutoff 128 s) and low-pass filtering.

Statistical analysis was performed using the general linear model as implemented in SPM5. For each subject, a design matrix was created using a canonical hemodynamic-response function for modeling the response to each of the conditions such as 'food', 'pleasure', and 'neutral', and the interaction 'food minus neutral'. Main effects and interactions between conditions were calculated separately on a single subject level using fixed effect analysis. Contrast images of each subject were subsequently used for group statistics calculated as random effects analysis at the second level, which takes variance between subjects into account. The statistical threshold used to report group activations was set as $P<0.05$ corrected for whole brain and for regions of interest (false discovery rate).[40] These comprised limbic/paralimbic areas (ventral (VLPFC, VMPFC) and dorsal PFC, ACC, amygdala, insula, hippocampus), basal ganglia (caudate, putamen (nucleus accumbens)), and diencephalic regions (hypothalamus, thalamus). In the absence of any masque for the nucleus accumbens, we took the striatum as region of interest, as the nucleus accumbens lays in the fusion part of the putamen and the caudate.[32] All regions were detected with the 'Automated Anatomical Labelling' software.[41]

In addition, we performed a repeated-measures analysis of variance for the within-factor STIMULUS (neutral, pleasant, food) and the between factor GROUP (normal weight, obese) on the BOLD magnitude of the highest activated voxel in regions of interests reaching significance in the interaction normal weight versus obese for the food condition, as revealed in the SPM analysis. To explore which brain regions might be associated with the autonomic indices of orienting (heart rate deceleration) evoked by food cues, we performed a regression analysis, as implemented in SPM5, for the food picture condition, using heart rate deceleration as a covariate.

Finally, regions with significant between-group differences were illustrated using the MRIcron software (http://www.sph.sc.edu/comd/rorden/mricron) by overlapping SPM5-activation maps on the segmented MNI-reference brain.

Psychological and physiological data. Only 17 children of each group completely filled out the FSK Questionnaire. Thus, only 34 subjects could be included in the statistical analysis, which was conducted on SPSS 12.0 (Statistical Package of the Social Sciences; SPSS for Windows; SPSS Inc., Chicago, IL, USA) using the non-parametric Wilcoxon test with a 0.05 level of significance. Interbeat (R-R) intervals were converted to heart rate (beats per minute) in half-second bins. Baseline heart rate (4-s preblock) was subtracted from the heart rate for every half-second during the first 6 s of the presentation of each picture. As an index for heart rate deceleration evoked by the pictures, we took the maximal deflection starting 2 s after the onset of picture presentation (the so-called D2 as an autonomic index of the orienting response.[42] Two normal-weight controls were not able to complete the second session, when physiological recordings were taken. Thus, only 20 subjects of each group were included in the statistical analysis. Statistical tests of heart rate data were completed with SPSS using the non-parametrical Wilcoxon test with a 0.05 level of significance.

Table 2 Regions of significant differences between obese and normal-weight subjects for food stimuli ($P<0.05$, FDR corrected for whole brain, >10 voxel)

Contrast	*Region*	*BA*		*MNI coordinates*				*t*
				x	*Y*	*z*		
Overweight > normal weight								
Food	DLPFC	9	L	−33	27	33	ROI	3.23*
Normal weight > overweight								
Food	Middle occipital gyrus	18	L	−24	−102	3		5.17
		18	R	39	−90	6		5.15
	Fusiform gyrus	37	L	−33	−48	−15		4.60
		19	R	33	−51	−9		5.40
	ACC	24	L	−6	24	15	ROI	3.32*
	Caudate		R	15	−18	21	ROI	3.32*
	Hippocampus		L	−33	−21	−21	ROI	3.25*
	Parahippocampal gyrus	19	R	30	−45	−6	ROI	4.04*
			L	−33	−24	−21	ROI	3.45*
	Thalamus		L	−15	−27	−3	ROI	3.86*

Abbreviations: ROI, region of interest; BA, Brodmann's area. *$P<0.001$ uncorrected.

Results

fMRI data

Whole brain analysis within each group. As expected, whole brain within-group analyses for food compared with neutral pictures yielded significant activation in the primary gustatory cortex (insula, inferior frontal operculum), areas of the orexigenic network (VLPFC, insula, hippocampus), and additional regions of the precentral and occipito-temporo-parietal cortex in both groups (see Supplementary Table 1). However, while only normal-weight children showed activation in the putamen and the amygdala, activation of middle frontal regions was only obvious in obese children.

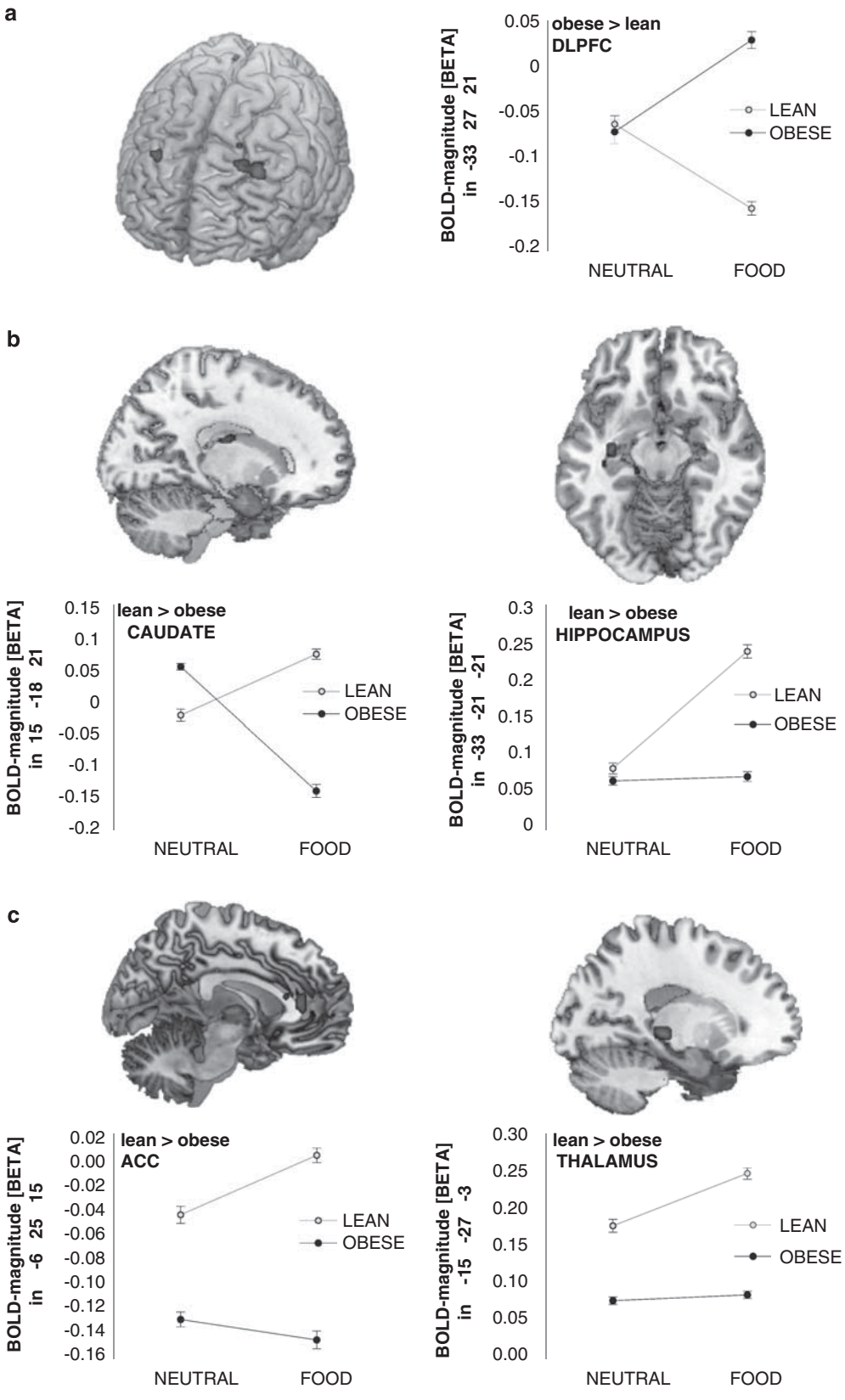
The within-group analysis for pleasant pictures minus neutral pictures yielded greater activation in typical areas associated with high positive valence, such as occipito-temporal regions, insula, and amygdala (for detailed regions, see Supplementary Table 2). Importantly, these activation patterns were identical for overweight and lean children. Furthermore, the DLPFC showed no activation during observation of pleasant stimuli in obese children.

Between-group analysis during viewing of food cues. Food pictures exhibited a significantly stronger activation of the left DLPFC in obese versus normal-weight subjects (see Table 2; Figure 1). We also found a tendency for greater activation in the right DLPFC ($T=2.65$; $P=0.006$; coordinates: 33, 39, 39). No other regions showed any significant activation in this between-group comparison. Comparing frontal brain activity evoked by neutral, pleasant, and food pictures between both groups in a more detailed analysis of the highest activated voxel within the DLPFC revealed a significant stimulus × group interaction [$F(2,41)=4.13$; $P=0.023$]. *Post hoc t*-tests showed a significant effect for the comparison DLPFC between subject groups for the food pictures ($t(42)=3.33$; $P<0.005$), but not for the neutral ($t(42)=0.11$; n.s.) or pleasant pictures ($t(42)=0.51$; n.s.).

In contrast, lean versus obese children showed significantly stronger activations in multiple areas during the viewing of food pictures. These comprised the ACC, the thalamus, the caudate, the hippocampus/parahippocampal gyrus, and additional areas of the visual cortex (middle occipital and fusiform gyrus) (see Table 2; Figure 1). Detailed analyses of the most activated voxels revealed a significant stimulus × group interaction in the caudate [$F(2,41)=6.35$; $P=0.004$] and the hippocampus [$F(2,41)=3.67$; $P=0.034$]. *Post hoc t*-tests for the caudate revealed a significant effect between subject groups for the food pictures ($t(42)=3.42$; $P<0.001$), but not for the neutral or pleasant pictures. The same was observed for the hippocampus ($t(42)=3.21$; $P<0.005$). This suggests that these paralimbic structures are stronger activated during viewing of food cues compared with neutral and pleasant pictures in normal weight, but not obese children. Again, these between-group differences supported the findings in the within-subject analysis.

Moreover, lean children showed overall (that is independent of stimulus type) stronger activation in the ACC (analysis of variance: [$F(2,41)=14.43$; $P=0.001$]; *post hoc* tests: $t(42)=2.67$; $P=0.01$) and the thalamus (analysis of variance: [$F(2,41)=17.51$; $P=0.001$]; *post hoc t*-tests: thalamus $t(42)=3.01$; $P=0.003$), relative to obese children. These areas are generally associated with attention and arousal.

Time of day comparison. When testing the effect of morning versus afternoon sessions for all subjects (25 were measured in the morning (8 a.m. to 12.20 a.m.) and 19 in the afternoon (12.30 a.m. to 6 p.m.)), we found a significant increase only for the left VLPFC (BA 47; $T=3.74$; $P<0.001$;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coordinates: −51, 33, –12) for the afternoon minus morning sessions during the food condition. This VLPFC activation was not specific for food stimuli, but was also found during the pleasant condition ($T=2.69$; $P<0.001$; coordinates: −45, 15, –6). No DLPFC activation was significant for the time of day comparison.

Effect of the last meal. We compared activation maps in response with food stimuli of those subjects (obese and normal weight) who were measured in the first 2 h after food intake (no matter whether breakfast or lunch) with those who were >2 h food deprived and observed no significant differences, but only sub-threshold activation in the bilateral insula ([$T=2.95$; $P=0.003$; coordinates: −33, 0, 12], [$T=2.63$; $P=0.006$; coordinates: 36, 6, 3]).

Correlation analysis

Heart rate. Heart rate deceleration evoked by food pictures was significantly correlated with the neural activation of a cluster in the VLPFC for the combined group of obese and normal-weight subjects (MNI coordinates: 39, 39, –3; $T=3.01$; see Figure 2). No other brain regions showed any significant correlations with heart rate changes, suggesting that this frontal brain region was significantly

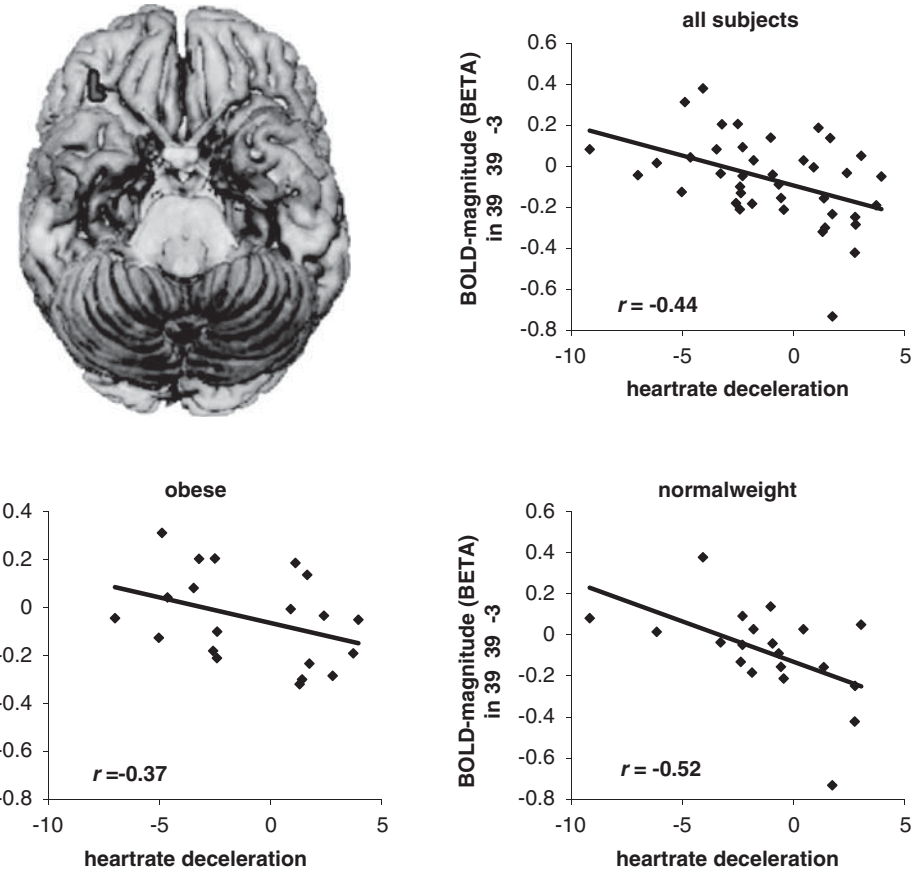

Figure 2 Negative correlation between brain activity in the VLPFC and deceleration of heart rate in obese and normal-weight subjects. Left top: BOLD magnitude in right VLPFC correlating highest negatively with the heart rate deceleration projected on the MNI-reference brain (bottom view). Right top: Correlation plot of BOLD magnitude in the highest activated voxel in the VLPFC with heart rate decelaration for all subjects ($n=44$). Correlation coefficient $r=-0.44$. Left bottom: Correlation plot of BOLD magnitude in the highest activated voxel in the OFC with heart rate decelaration for obese subjects ($n=22$) did not show a significant correlation ($r=-0.37$). Right bottom: Correlation plot of BOLD magnitude in the highest activated voxel in the VLPFC with heart rate decelaration for normal-weight subjects ($n=22$) showed a significant negative correlation ($r=-0.52$).

Figure 1 Areas of significant between-group differences during the food condition (for display purpose, we lowered the threshold to $P<0.01$). Illustration of the mean BOLD magnitude plus standard error within these regions for the neutral and food conditions in obese and lean subjects. (**a**) Significantly higher activation of the DLPFC in obese children compared with that in normal-weight children, specific to food pictures. (**b**) Significantly higher activation of the caudate nucleus and the hippocampus in normal-weight children compared with that in obese children, specific to food pictures. (**c**) Significantly higher activation of the ACC and the thalamus in normal-weight children compared with that in obese children, which is not specific to food pictures, but to visual cues in general.

associated with increased autonomic orienting evoked by the food cues.

Self-esteem. Self-esteem was also significantly negatively correlated with activation of the DLPFC ($r=-0.287$; $P=0.05$) for the combined group of obese and normal-weight subjects. This suggests that prefrontal control was increasingly active during viewing of food cues in children with lower reported self-esteem. Obese children reported significantly less self-esteem than lean control children ($z(34)=3.09$; $P=0.02$).

Affective ratings

Overall, pleasant and food pictures were rated as significantly more pleasant than the neutral pictures (Wilcoxon $z(40)>2.10$; $P<0.05$), validating the preselection procedure. Importantly, both groups rated the pictures as equally pleasant and arousing ($t(38)<1.1$; n.s.), suggesting that there was no difference in the emotional responses of each group to the pictures.

Discussion

Normal-weight children responded to visually presented food stimuli with a high blood oxygenation level-dependent magnitude in areas associated with emotional processing (insula, VLPFC), reward areas such as the ventral striatum, and regions that are targets of these reward centers (amygdala and hippocampus). In contrast, children with obesity show increased dorsal PFC activity during the perception of food. Altered cerebral activation was accompanied by decreased autonomic orienting in response to food stimuli, as indexed by heart rate.

Our results are consistent to those imaging studies, reporting a decrease of activation in areas related to emotional processing in obese adolescent subjects.[28–30] The finding of increased neural activation of the putamen and the amygdala in lean compared with obese children may suggest that obese children have difficulties in activating their reward system by food cues. Directly comparing brain activation in response to food pictures in obese and normal-weight children yielded significant stronger activations of the caudate, the hippocampus/parahippocampal gyrus, the ACC, the thalamus, and the middle occipital and fusiform gyrus in normal-weight children. These results point to increased vigilance in normal-weight children to the presented stimuli.

We found a significantly stronger activation in obese versus normal weight in response to food cues in the dorsal part of the PFC, located at the border between medial and lateral areas. This finding was specific for food stimuli, as no DLPFC activation was seen for the pleasant condition (see Supplementary Table 2). The dorsal PFC is linked to numerous aspects of top–down control, especially 'executive functions', goal selection, planning, manipulation of information, and response inhibition. There is considerable evidence of a major function of the PFC in high-order control processes exerting a top–down regulation of cognition and behavior,[19,23,43,44] realized by different prefrontal–subcortical circuits.[21,45,46] According to Petrides,[47,48] our finding may correspond to the middorsolateral PFC (BA 9/46), an area that is responsible for high-order planning and the organization of behavior.

Activation of the PFC increases with a rising amount of conflict, regardless whether it is emotional or cognitive.[49] Food cues might provoke a higher conflict situation in obese children, as they only showed a higher PFC activation during the food condition. In response to neutral and also to pleasant pictures, there was no difference in the PFC activation between lean and obese children. PFC activation is especially important in situations with competing behavioral alternatives and serves to suppress the stronger and more salient one. However, this may result in inappropriate behavior.[23] Therefore, in obese children, PFC activation may suppress the appetitive reaction or approach behavior in response to food cues, leading to avoidance.[50] The increased DPFC activation in obese children points to an avoidance process associated with the presented food stimuli. The more there is need for inhibitory control, the greater is the activation in the PFC,[23,51] indicating that in obese children, confronted with food cues, a stronger top–down control of PFC on subcortical regions is necessary to produce the appropriate behavior, that is not to eat, regardless of whether they are hungry or not. Accordingly, the lower the self-esteem, the stronger the activation of the prefrontal top–down control system. These data suggest that obese children already have a strong goal not to overeat, and, therefore, inhibit their food-related reward system, which might then increase depressive mood and lower self-esteem.

Our results are also consistent with earlier neuroimaging studies in adults that found a greater activation of prefrontal areas in response to food cues in satiated obese versus lean individuals.[28,29] The prefrontal areas have been termed as a 'satiation domain', inducing the termination of a feeding period by suppressing subcortical 'orexigenic areas', such as limbic/paralimbic areas, basal ganglia, the thalamus, and the hypothalamus.[24,25] In obese people, the orexigenic network is chronically hyperactive, requiring the prefrontal areas to work harder to suppress these hunger centers.[24,25]

In contrast, normal-weight children tend to respond more physiologically to food cues, showing a stronger appetitive or approach reaction, as indicated by their significant higher activation of the caudate and the hippocampus only during the food condition. Rewarding stimuli, that is food cues, are known to facilitate approaching behavior, mediated by the dorsal striatum.[52–54] Moreover, the significantly stronger activation of the nucleus caudatus, a part of the dopaminergic brain reward system, in lean children solely during the food condition implies that food cues may be experienced as less

rewarding by obese children, as postulated by reward deficiency syndrome.

Another brain region strongly linked to food approach behavior is the hippocampus.[55,56] On the basis of the detection and integration of energy state signals and by encoding and memorally representing a variety of information about food experiences, it has a major function in the control of feeding behavior.[57] Thus, a less appropriate functioning hippocampus may also be a risk factor for obesity, as obese children had a significant lower activation of the hippocampus than lean children, specifically in response to food cues. Our findings in children correspond to earlier neuroimaging studies in adults, which also showed significantly less hippocampal activation in obese subjects in response to food cues.[30,58]

The thalamus and the ACC are both brain regions involved in several aspects of attention, showing a stronger activation during task-relevant events, contributing to the identification of behaviorally important environmental stimuli.[59] Although the thalamus corresponds to the alerting component of external cues and is strongly associated with arousal and emotional content,[60,61] the ACC is more involved in the executive control of attention. The ACC assesses the motivational content of internal and external stimuli regulating context-dependent behaviors.[60,62,63] As we found a significantly greater activation of the ACC and the thalamus in normal weight versus obese children in response to external cues independent of stimulus type (food or neutral), we postulate that normal-weight children generally respond to all environmental stimuli or task information. This might be associated with a decreased inhibitory top–down control of prefrontal regions.

Consistent with our finding of more attentive reactions of lean children to external stimuli is the tendency of lean children to show a stronger autonomic orienting response, as reflected in the heart rate deceleration in response to food stimuli. In contrast, obese children tend to react with heart rate acceleration. Heart rate deceleration is a major component of the orienting response to external stimuli, corresponding to an increased sensitivity to stimulation and occurring in response to pleasant stimuli or when situations demand attention. In contrast, heart rate acceleration is associated with a decrease in sensitivity to stimulation, happening during unpleasant stimuli, should ease the 'rejection of the environment', and should occur in 'situations in which external distractions would interfere with internal problem solving'.[64,65] Our finding of a positive correlation between increased heart rate deceleration and increasing activity in VLPFC indicates that the more intense the orienting response especially to food cues, the greater the activation of the VLPFC. This correlation is stronger in normal-weight children than in obese children, stressing the higher reactivity of lean children to external stimuli, especially during the food condition. As the OFC (respectively VLPFC or/and VMPFC) is a convergence area for olfactory, gustatory, and visual food stimuli,[66] it is a brain area closely linked to the processing of food and the regulation of eating behavior.[67] Implemented in evaluating positive reinforcers and in detecting the rewarding value of food,[68,69] OFC activity has been shown to correlate positively with subjective feelings of hunger and desire for food.[70,71] The negative correlation between BMI and OFC activation[72] indicates that the OFC is essential for food intake regulation. Thus, the weaker orienting response and the less strong correlation of heart rate change to VLPFC activity in obese may also represent risk factors of obesity, reflecting disturbances in food intake regulation ability.

This study has several limitations. One is our approach to use a 'real life situation' with different measurements roughly balanced in respect to food intake and time of day between subject groups without using more standardized methods such as providing a standardized meal before scanning after one night of fastening. This did certainly weaken the results between subject groups. However, we tested the effect of morning versus afternoon sessions and found only a significant increase for the left VLPFC (BA 47) for the afternoon minus morning sessions. This increased BA47 activation might be associated with a more vivid emotional perception, as it was unspecific for food stimuli, but also seen for the afternoon–morning comparison for the pleasant stimuli. The VLPFC has been shown to be associated with differences in the perceived dimension of valence, which is unspecific to the modality (for the visual modality: Lotze *et al.*, 2006[73]; for the auditory modality: Wildgruber *et al.*, 2004[74]). For the time of day comparison, no DLPFC activation was significant. Another issue is the known modulation of BOLD-signal magnitude by hunger.[24–26] We compared activation maps in response to food stimuli between all subjects measured in the first 2 h after food intake (no matter whether breakfast or lunch) and those who did not eat >2 h before fMRI scanning. This comparison revealed sub-threshold activation in the bilateral insula. Therefore, the effect of increased DLPFC activation of obese children to food stimuli is neither dependent on the time of day nor on the hunger condition of the subject, but specific for obese children.

Another limitation is a problem in general with investigations of patients enrolled in a therapeutic intervention: the emotional response is highly influenced by the knowledge of the aim of the therapy. This might have certainly influenced the emotional processing of food stimuli in this investigation, too.

In conclusion, our results indicate that obese children react with a high inhibitory control to food stimuli, but show decreased psychophysiologic response (heart rate deceleration) to emotional stimuli in general. This inhibitory top–down control is exerted by the DLPFC, suppressing the activation of subcortical structures, diminishing their ability to detect the rewarding value of external cues, and to integrate internal body state information. Hence, because of their strong inhibitory control, obese children cannot be easily affected by external cues and reconcile them with

internal body needs. This results in early disorders of food intake regulation and eating behavior, consequently contributing to obesity. In future studies, it would be interesting to further investigate top–down control and assess the effective connectivity between prefrontal and subcortical regions. It would also be valuable to measure the directionality of signaling in these networks using recently developed analytic techniques, such as dynamic causal modeling or granger causality mapping.

Conflict of interest

The authors declare no conflict of interest.

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