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Childhood maltreatment moderates the influence of genetic load for obesity on reward related brain structure and function in major depression

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ABSTRACT

Obesity is a clinically relevant and highly prevalent somatic comorbidity of major depression (MDD). Genetic predisposition and history of childhood trauma have both independently been demonstrated to act as risk factors for obesity and to be associated with alterations in reward related brain structure and function. We therefore aimed to investigate the influence of childhood maltreatment and genetic risk for obesity on structural and functional imaging correlates associated with reward processing in MDD. 161 MDD patients underwent structural and functional MRI during a frequently used card guessing paradigm. Main and interaction effects of a polygenic risk score for obesity (PRS) and childhood maltreatment experiences as assessed using the Childhood Trauma Questionnaire (CTQ) were investigated. We found that maltreatment experiences and polygenic risk for obesity significantly interacted on a) body mass index b) gray matter volume of the orbitofrontal cortex as well as on c) BOLD response in the right insula during reward processing. While polygenic risk for obesity was associated with elevated BMI as well as with decreased OFC gray matter and increased insular BOLD response in non-maltreated patients, these associations were absent in patients with a history of childhood trauma. No significant main effect of PRS or maltreatment on gray matter or BOLD response could be detected at the applied thresholds. The present study suggests that childhood maltreatment moderates the influence of genetic load for obesity on BMI as well as on altered brain structure and function in reward related brain circuits in MDD.

1. Introduction

Obesity is a highly prevalent comorbidity of affective disorders that has been shown to predict unfavorable outcomes in major depressive disorder (MDD) patients (de Wit et al., 2010; Kloiber et al., 2007; Luppino et al., 2010; Opel et al., 2015b; World Health Organization, 2014). In turn, findings indicating that both maternal depression and family history of obesity might increase the risk of non-response to weight-regulating interventions further corroborate the notion of a reciprocal link between obesity and depression and point to the relevance of shared genetic factors in the etiology of both conditions (Epstein et al., 1994; Pott et al., 2009). In addition, environmental risk factors such as childhood maltreatment and socioeconomic status have been suggested to influence the association between obesity and depression (Danese and Tan, 2014; Molyneaux et al., 2016; Simon et al., 2006).

More concrete, previous research has independently identified genetic predisposition as well as adverse environmental conditions such as childhood maltreatment as important risk factors in the development of obesity in healthy subjects (Danese and Tan, 2014; Hughes et al., 2017; Locke et al., 2015). However, up to now little is known about the

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biological underpinnings that underlie excessive weight gain in major depression. More specifically, to date no study is available that accounted for the influence of both genetic risk and childhood maltreatment on BMI in major depression.

Regarding potential mechanistic relationships that might mediate the development of excessive weight gain, multiple previous reports have pointed to the importance of altered structure and function of reward related brain areas in obesity (Batterink et al., 2010; Opel et al., 2015b; Raji et al., 2010). More specifically, obesity has repeatedly been associated with structural and functional alterations in the orbitofrontal cortex (OFC), the ventral striatum and the cingulate cortex as well as sensory regions including the insula (Burger and Stice, 2014; Smith and Robbins, 2013; Stice et al., 2011). The specific importance of prefrontal gray matter reductions in obesity is further corroborated by recent work by our group that a) demonstrated that OFC gray matter volume reductions associate with BMI in both healthy and depressed subjects (Opel et al., 2015b) and that b) polygenic load for obesity correlates with brain structural volume decline in the OFC in healthy subjects suggesting that prefrontal alterations could mediate the genetic influence on BMI (Opel et al., 2017a, b).

Interestingly, independent evidence from functional and structural neuroimaging research has also pointed to associations between childhood maltreatment as well as MDD and altered reward processing suggesting structural brain changes in partly similar regions within the orbitofrontal cortex (OFC) in childhood maltreatment (Dannlowski et al., 2012; Lim et al., 2014; Nemeroff, 2016) and MDD (Drevets, 2007; Phillips et al., 2003; Price and Drevets, 2012; Rive et al., 2013). Considering the key role of the OFC in neurocognitive domains such as emotion regulation, reward processing and impulse control, it appears highly suggestive to assume the OFC and associated reward related brain areas in the center of a shared neurobiological background that might underlie the clinical association between genetic risk for obesity, maltreatment and weight gain in MDD.

Altogether, it thus appears plausible to assume that both genetic and early environmental risk factors influence reward related brain structure and function which could then lead to increased susceptibility for the development of obesity in MDD.

However, up to now the influence of genetic load and maltreatment experiences on body weight as well as on brain structural and functional alterations in MDD remains uncertain. With the present study, we sought to investigate the role of both genetic risk and maltreatment experiences on BMI as well as on brain structure and function associated with obesity in MDD. Regarding the evidence for the contribution of gene x environmental interactions on clinical phenotypes (Byrd and Manuck, 2014) as well as on brain structure and function in maltreated individuals (Dannlowski et al., 2016) from other fields of research, we aimed to test possible main and interaction effects of polygenic load for obesity and childhood maltreatment on BMI and reward related brain imaging correlates. In light of the aforementioned evidence from the literature and from our previous work (Opel et al., 2017a, b; Opel et al., 2015b), we hypothesized that polygenic load for obesity and maltreatment experiences would be associated with BMI as well as with structural and functional alterations in brain areas related to reward processing, first and foremost in the orbitofrontal cortex.

2. Materials and methods

2.1. Participants

Our initial study sample comprised 161 MDD patients recruited at the Department of Psychiatry at the University Hospital of Münster as part of the Münster Neuroimage Cohort (MNC) (see Table 1 for socio-demographic and clinical characteristics).

All MDD patients included in the present study were under current inpatient treatment at the University Hospital of Münster. All but 10 participants received antidepressant medication at the time of the study. All patients received psychotherapeutic treatment as part of the usual inpatient care routine. None of the included participants received electroconvulsive therapy (ECT) at the time of study participation and only two participants had received ECT during prior treatments. Information on weight and height were based on self-reports from each participant.

For all subjects, exclusion criteria were any history of neurological (e.g., concussion, stroke, tumor, neuro-inflammatory diseases) and medical (e.g., cancer, chronic inflammatory or autoimmune diseases, heart diseases, diabetes mellitus, infections) conditions. All subjects 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, 2005)). All participants received a financial compensation. The study was approved by the local IRB, and written informed consent was obtained from all participants before study participation. Clinical diagnoses in all depressed patients were obtained using the DSM-IV Structured Clinical Interview (SCID-I) (Wittchen et al., 1997). To assess the current level of depressive symptoms the Hamilton Rating Scale for Depression (HAM-D) (Hamilton 1960), and the Beck Depression Inventory (BDI) (Beck & Steer 1987) were administered.

2.1.1. Assessment of medication load

To assess the influence of psychopharmacological therapy in the MDD sample, type and dose of psychopharmacological treatment was recorded to compute a medication index by applying a strategy described in our previous work (Redlich et al., 2014). Each psychotropic medication was coded as absent = 0, low = 1 (equal or lower average dose), or high = 2 (greater than average dose), relative to the midpoint of the daily dose range recommended by Physician's-Desk-Reference. A composite measure of total medication load was calculated for each individual, reflecting dose and variety of different medications taken, by summing all individual medication.

2.1.2. Assessment of maltreatment experiences

Presence and level of childhood maltreatment were evaluated using the Childhood Trauma Questionnaire (CTQ) assessing 5 types of adverse early life experiences by means of a 25-item retrospective self-report questionnaire (Bernstein et al., 1994). CTQ dichotomous cut-off scores were applied to distinguish subjects who experienced significant forms of abuse and neglect (CM+) from non-maltreated individuals (CM-) as proposed by Walker et al. (Walker et al., 1999). Following this approach a subject was classified as having experienced significant forms of former childhood abuse or neglect if the person reached a predefined score for at least one of the five CTQ subscales (cut-off scores for each subscale: physical abuse > 8, sexual abuse > 8, physical neglect > 8, emotional abuse > 10, emotional neglect > 15) (Walker et al., 1999). The applied cut-off scores have previously been externally validated by direct comparison with assessment of childhood trauma via structured interviews and were demonstrated to detect former maltreatment experiences with sensitivity and specificity rates of > 0.85 for each subscale (Walker et al., 1999).

2.2. sMRI methods

2.2.1. Image acquisition

T1-weighted high-resolution anatomical images were acquired (Gyroscan Intera 3 T, Philips Medical Systems, Best, NL) using a three-dimensional fast gradient echo sequence (turbo field echo), with a repetition time of 7.4 ms, echo time = 3.4 ms, flip angle = 9°, two signal averages, inversion prepulse every 814.5 ms, acquired over a field of view of 256 (feet-head) x 204 (anterior-posterior) x 160 (right-left) mm, phase encoding in AP and RL direction, reconstructed to voxels of 0.5 mm *x* 0.5 mm *x* 0.5 mm.

Table 1
Sociodemographic and clinical characteristics of our study sample consisting of 161 MDD patients, divided into a subsample of n = 108 subjects with (CM+) and n = 53 subjects without childhood maltreatment experiences (CM-). Means, standard deviations (± SD) and group differences between CM + and CM- subjects (as measured with t-tests or Chi²-tests).

	Total sample (n = 161)		CM+ (n = 108)		CM- (n = 53)		p-value
	Mean	± SD	Mean	± SD	Mean	± SD	
Age	37.36	11.81	38.03	12.03	35.98	11.36	.301
Sex (m/f)	71/90		44/64		27/26		.220
BMI	25.77	4.87	25.74	4.87	25.83	4.92	.917
HAMD	22.91	4.98	23.35	5.06	22.02	4.75	.113
BDI	27.76	9.11	28.98	9.37	25.28	8.07	.015
IQ	110.35	13.68	109.66	14	111.78	13.01	.358
CTQ total	46.29	17.1	53.72	16.15	31.15	3.75	< 0.001
Medication load	2.29	1.44	2.22	1.47	2.43	1.41	.383
Medication type:							
SNRIs	73		47		26		.507
SSRIs	40		27		13		.948
NaSSAs	36		25		11		.729
Tricyclic ADs	6		4		2		.982
Mood Stabilizer	11		7		4		.801
Antipsychotics	59		35		24		.111

2.2.2. VBM

The CAT12-toolbox (http://www.neuro.uni-jena.de/cat/). Image quality was assessed by visual inspection as well as by using the check for homogeneity function implemented in the CAT12 toolbox. 5 subjects were excluded due to poor image quality (mean correlation < 2 SDs) or anatomical artefacts, leaving a total of n = 156 subjects for all sMRI analyses.

2.3. fMRI methods

2.3.1. Stimulus materials and procedure

We employed a modified, frequently used card guessing paradigm (Delgado et al., 2005; Forbes et al., 2009) as employed recently (Opel et al., 2015a; Redlich et al., 2015) 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 9 blocks: 3 "win" blocks (block 1, 4, 7), 3 "lose" blocks (block 2, 5, 8) and 3 control blocks (block 3, 6, 9) with each block consisting of 5 trials. During each trial, subjects had 3 s (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 et cetera) or 2.5 s for consecutive even-numbered stimuli throughout the whole paradigm (i.e. for the second, fourth, sixth stimuli et cetera), 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.

2.3.2. fMRI data acquisition and analysis

T2* functional data were acquired using the same scanner and 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 x 3.6 mm x 3.6 mm; TR = 2.1 s, TE = 30 ms, FA = 90°). The slices were tilted 25° from the AC/PC line in order to minimize drop out artifacts in the mediotemporal and orbitofrontal region.

Data were analyzed using statistical parametric mapping software (SPM12, 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 (FWHM) as described in our previous work (Dannlowski et al., 2015; Donges et al., 2012; Opel et al., 2017a, b).

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 (GLM) including corrections for serial correlations and application of a high-pass filter of 128 s to remove low-frequency noise.

For each subject, 1st-level analyses were conducted yielding a contrast-image for "win > control" which were used for all subsequent 2nd-level analyses. Failure to acquire fMRI data, fMRI-related artifacts, or excessive head movement (exclusion criterion > 3 mm and/or 3°) led to an additional exclusion of 18 subjects, leaving a total of n = 138 complete datasets for all fMRI analyses. Main effects of the applied fMRI contrast (win > control) were assessed in the final sample and are displayed in Supplementary Fig. 1.

2.4. Genetic methods

2.4.1. Polygenic risk score

Genotyping in all subjects was performed using previously published protocols (see Supplementary Methods) (Dannlowski et al., 2015; Opel et al., 2017a, b).

A polygenic risk score (PRS) for obesity that has previously been shown to be associated with BMI and prefrontal gray matter in healthy subjects (Opel et al., 2017a, b) was generated using all available SNPs (p-value threshold at 1.0) from the base GWAS data (Locke et al., 2015). The R program "PRSice" (Euesden et al., 2015) which uses

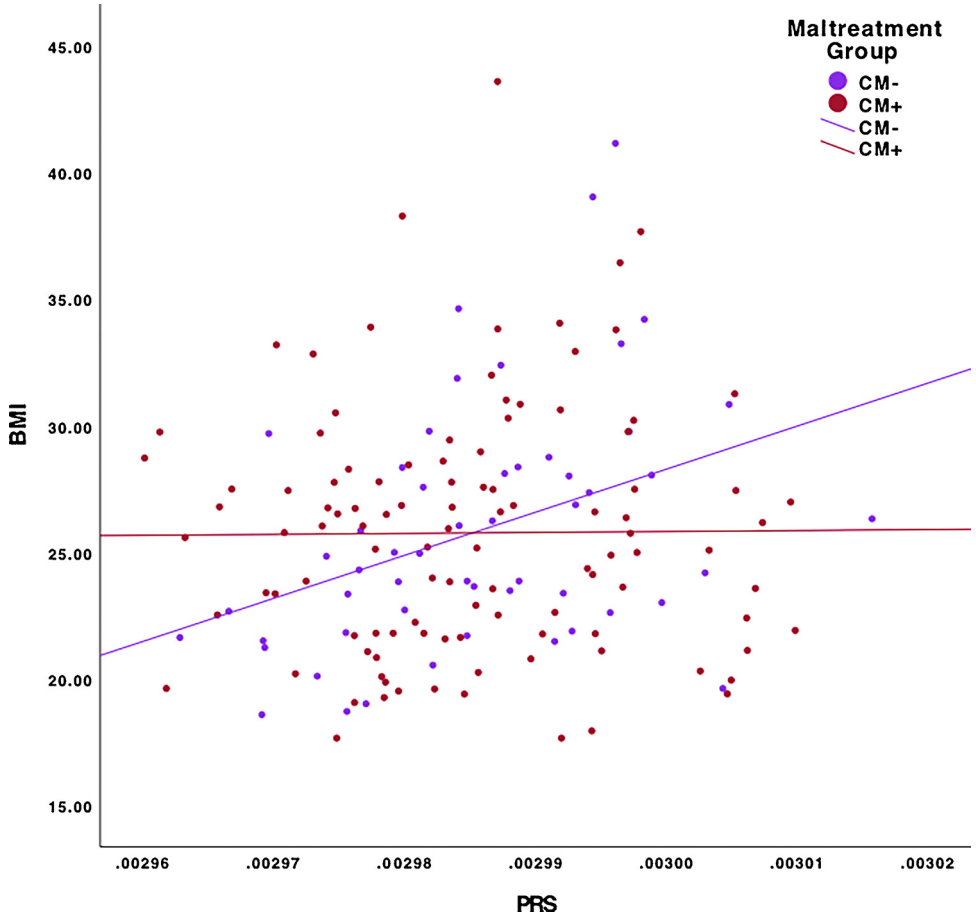

Fig. 1. Interaction of PRS and maltreatment on BMI: Plot depicting associations between PRS and BMI in the CM- and CM + groups; Abbreviations: BMI, body mass index, CM-, non-maltreated subjects, CM + maltreated subjects, PRS, Polygenic Risk Score.

PLINK-1.9 (Chang et al., 2015) in the background for linkage disequilibrium pruning was used for this analysis. The influence of the polygenic risk score on BMI was assessed by using linear regression analyses: First a base model including age and sex as independent variables and BMI as dependent variable was created which accounted for 9% of the variance in BMI (R^2 = .09, $F_{(2,160)}$ = 7.85, p = .001). Including the polygenic risk score in the model led to an additional explained variance of 3.7% (R^2 = .127, R^2-change = 0.037, $F_{(3, 160)}$ = 7.58, p < .001) obtained through a significant positive association between the PRS and BMI (β = .197, p = 0.012).

2.5. Statistical analyses

SPSS (IBM) version 25 was used for all statistical analyses except for imaging analyses which were performed using SPM12 (http://www.fil.ion.ucl.ac.uk/spm).

In order to address our hypotheses the following analyses steps were carried out:

2.5.1. Clinical variables

To explore possible main and interaction effects of polygenic risk for obesity and maltreatment on BMI an analysis of covariance (ANCOVA) was applied including PRS and maltreatment group (CM + /CM-) as well as the interaction term of PRS x maltreatment as independent variables, age and sex as nuisance regressors and BMI as dependent variable.

2.5.2. sMRI analyses

VBM analyses were performed with a corresponding design by applying a full factorial model including maltreatment group (CM + /CM −) as between-subjects factor, PRS scores as covariate, the interaction term of maltreatment group x PRS, as well as age, sex and total intracranial volume (TIV) as nuisance regressor.

2.5.3. fMRI analyses

fMRI analyses were performed with a corresponding design by applying a full factorial model including maltreatment group (CM + /CM −) as between-subjects factor, PRS scores as covariate, the interaction term of maltreatment group x PRS, as well as age and sex as nuisance regressor.

Following our hypotheses VBM and fMRI analyses were a) first carried out as ROI analyses employing a mask of the entire orbitofrontal cortex with a rigorous family wise error (FWE)-correction on the voxel-level at p < 0.05. The OFC mask was created by means of the WFU PickAtlas (Maldjian et al., 2003) by including the bilateral mask of the orbital parts of the medial, the middle, the superior and the inferior frontal gyrus according to the AAL-Atlas (Tzourio-Mazoyer et al., 2002). b) Additionally, whole brain analyses with a cluster-level FWE corrected significance threshold for multiple testing at p < 0.05 were performed. The anatomical labeling was performed by means of the AAL-Toolbox (Tzourio-Mazoyer et al., 2002).

3. Results

3.1. Clinical results

A significant interaction effect of PRS and maltreatment on BMI occurred ($F_{(2, 160)}$ = 3.32, p = 0.039, η_p^2 = 0.041) which was driven

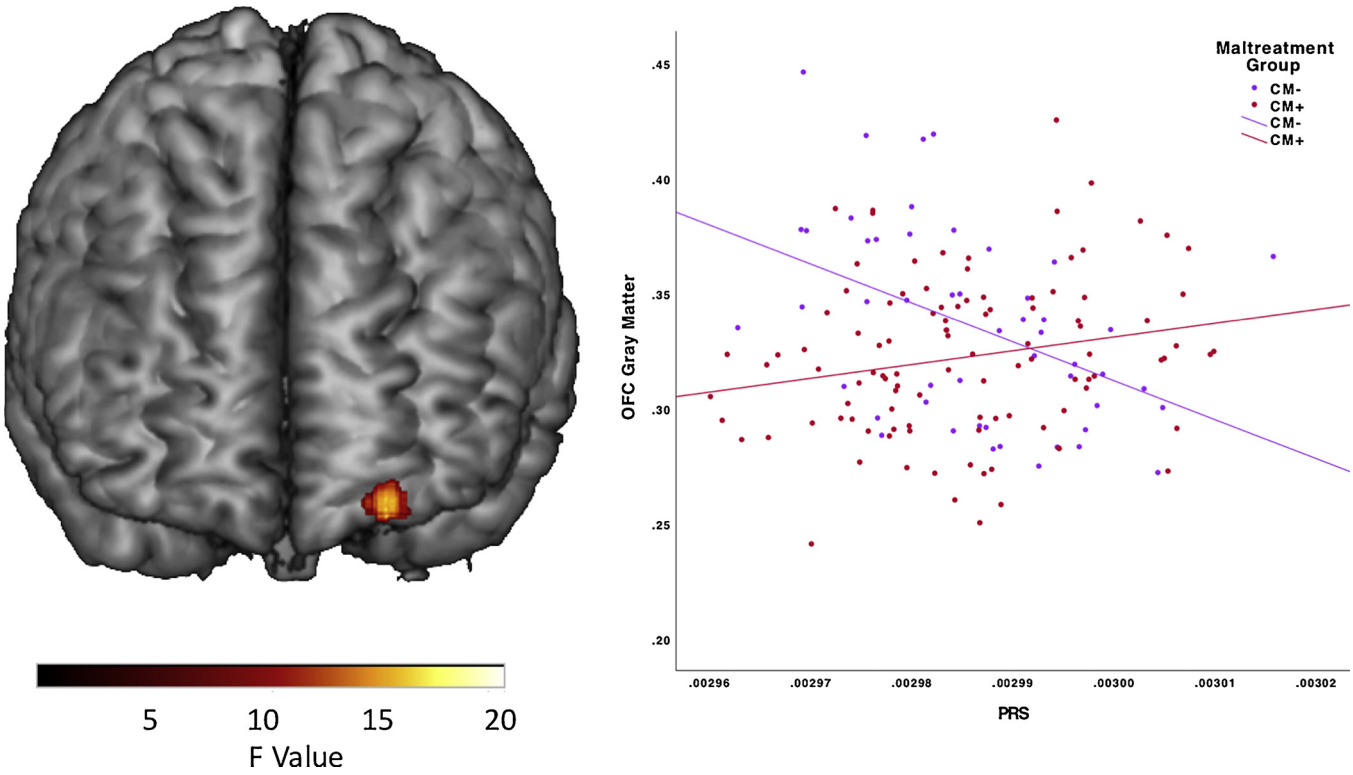

Fig. 2. Interaction of childhood maltreatment and PRS on OFC gray matter (mean gray matter value at MNI coordinates x = −24, y = 27, z = −24) (For display reasons values are thresholded at p = 0.001, k = 100). Abbreviations: MNI, Montreal Neurological Institute, PRS, Polygenic Risk Score, OFC, Orbitofrontal Cortex.

by a strong positive association between PRS and BMI in CM- individuals (CM- r = .382, p = .005, CM + r = .009, p = .926) (see Fig. 1). We furthermore observed a significant main effect of maltreatment on BMI ($F_{(1,160)}$ = 5.30, p = 0.023, η_p^2 = 0.033). No significant main effect of PRS could be detected in this analysis.

3.2. sMRI results

(1) The VBM ROI analysis yielded a significant interaction effect of PRS and maltreatment on gray matter in the orbitofrontal cortex (x = −24,y = 27,z = −24,$F_{(1,149)}$ = 19.85,k = 15,p_{FWE} = 0.020). The interaction effect was driven by a strong negative correlation between PRS and OFC gray matter in CM- subjects and a positive correlation in CM + subjects ((CM- r = −.44, CM + r = .20 at x = −24,y = 27,z = −24) (see Fig. 2). No significant main effect of maltreatment or PRS on OFC gray matter could be detected in this analysis. To control for the potential influence of psychotropic medication on the observed sMRI findings, analyses were repeated by including medication load as additional nuisance regressor yielding highly similar results with a still significant interaction of PRS and maltreatment on OFC gray matter (x = −24,y = 27, z = −24,$F_{(1,148)}$ = 19.67,k = 13,p_{FWE} = 0.022)

Additional validation analyses were carried out by using Freesurfer derived cortical thickness and surface measures of the orbitofrontal cortex which yielded a significant interaction effect of PRS and maltreatment on right lateral OFC surface area while no interaction or main effect on cortical thickness could be detected (see Suplementary Results and Supplementary Fig. 2 for details).

(2) No further supratreshold clusters could be detected in the additional VBM whole brain analyses for interaction or main effects of PRS and maltreatment.

3.3. fMRI results

(1) No significant interaction or main effects of PRS and maltreatment could be detected in the ROI analyses of OFC BOLD response during reward processing at the applied thresholds.

Whole brain analyses revealed a significant interaction of PRS and maltreatment on BOLD response in the right insula (x = 34, y = 16, z = −6, $F_{(1,132)}$ = 25.17, k = 170, p_{FWE} = 0.010) driven by a strong negative correlation between PRS and BOLD response in CM + subjects and a positive association in CM- subjects (CM- r = .-43; CM + r = .45 at x = 34, y = 16, z = -6) (see Fig. 3). No further suprathreshold clusters could be detected in the fMRI whole brain analyses for main effects of PRS or maltreatment.

(2) Again, we controlled for the influence of psychotropic medication, by including medication load as nuisance regressor. Still, a highly significant interaction of PRS and maltreatment on BOLD response in the right insula (x = 34, y = 16, z = −6,$F_{(1,131)}$ = 27.54, k = 193, p_{FWE} = 0.005) emerged.

3.4. Analyses of potential associations between sMRI and fMRI results

Finally, we aimed to investigate potential associations between the observed structural and functional findings. To this end, we assessed whether OFC gray matter might associate with BOLD response during reward processing. Mean gray matter values of the interaction effect of PRS and maltreatment were extracted from a sphere of 5 mm around the OFC peak voxel (x = −24,y = 27,z = −24;) of the VBM analysis of step 3.2.1. The extracted mean gray matter values were subsequently entered as independent variable in a new fMRI 2ndlevel multiple regression model including age and sex as nuisance regressors. This model did not reveal any significant positive or negative associations between OFC gray matter and whole brain BOLD response during reward processing. Even at an exploratory threshold of p = .001, k = 20 no suprathreshold clusters could be detected.

4. Discussion

With this study we provide evidence for an interaction of childhood

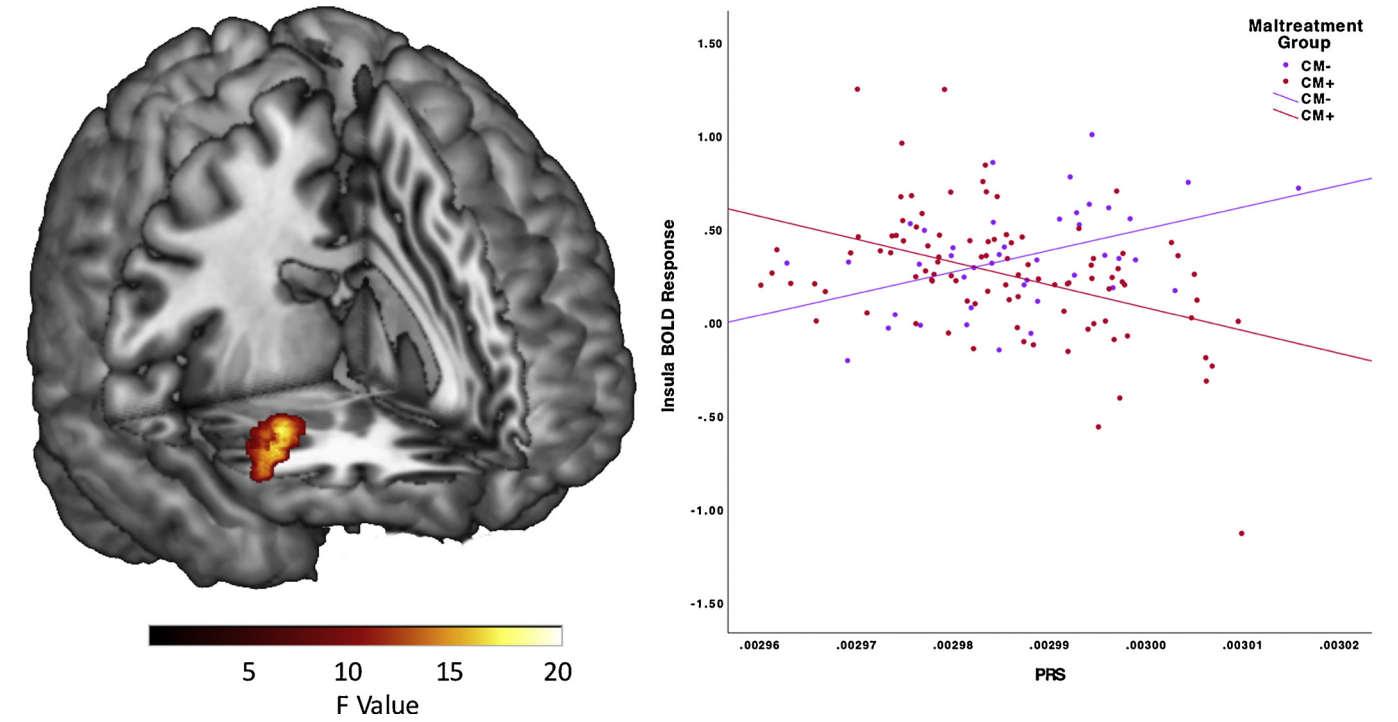

Fig. 3. Interaction of childhood maltreatment and PRS on BOLD response in the right insula (mean fMRI contrast value at MNI coordinates x = 34, y = 16, z = −6) (For display reasons values are thresholded at p = 0.001, k = 100). Abbreviations: MNI, Montreal Neurological Institute, PRS, Polygenic Risk Score, OFC, Orbitofrontal Cortex.

maltreatment and polygenic load for obesity on BMI as well as on brain structure and function of reward related brain circuits in major depression. These findings link genetic risk for obesity and maltreatment to the development of excessive weight gain in MDD on a clinical and neurobiological level.

Our study demonstrates that the influence of polygenic risk for obesity on BMI is moderated by maltreatment experiences in MDD patients. While polygenic risk for obesity predicted elevated BMI in non-maltreated patients, this association was absent in patients with a history of childhood trauma suggesting a concurring effect of both risk factors on weight gain in MDD. It thus appears that the presence of maltreatment as a decisive environmental risk factor erases the influence of genetic risk on BMI. This finding of a reduced impact of polygenic risk for obesity on BMI in the presence of maltreatment experiences adds insights into the biological underpinnings of obesity by highlighting the importance of considering both genetic and environmental risk factors in the development of obesity. Regarding potential explanations for our observation, it appears plausible that environmental and genetic risk factors for obesity might impose their influence on brain structure and function via differing and concurring neurobiological pathways. Early life stress has repeatedly been evidenced to impact brain structure and function, immune activation and neuroendocrine stress response (Danese et al., 2008; Frodl et al., 2017; Frodl and O'Keane, 2013; Heim et al., 2008; Opel et al., 2014; Stein et al., 2018) and is therefore thought to impose a strong impact on physiological neurodevelopmental processes. Following this notion, childhood maltreatment might interfere with genetically determined biological correlates of obesity. In this regard, it also appears relevant to emphasize that our work clearly underlines the relevance of two risk factors that precede the onset of weight gain in obesity by many years.

Importantly, our imaging results furthermore provide a potential mechanistic correlate that might underlie the observed gene x environmental interaction on BMI by demonstrating similar interaction effects of maltreatment and polygenic risk for obesity on common structural and functional imaging correlates of obesity within reward related brain areas. Corresponding to our clinical observation, the presented imaging analyses revealed that effects of polygenic risk for obesity on OFC gray matter decrease and increased BOLD response during reward processing were again restricted to the subgroup of non-maltreated subjects.

The relevance of these imaging correlates of obesity is confirmed by various previous studies indicating OFC gray matter decrease as well as altered reward processing to be among the most frequently reported findings in neuroimaging research on obesity (Batterink et al., 2010; Burger and Berner, 2014; Janowitz et al., 2015; Opel et al., 2015a; Raji et al., 2010; Shott et al., 2014). Additional analyses using Freesurfer based segmentations revealed a similar interaction effect of maltreatment and polygenic risk on surface area of the right lateral OFC, while no significant interaction effect on OFC thickness could be detected. We thus conclude that the presented structural findings might primarily be driven by cortical surface area alterations rather than by altered cortical thickness.

Further insights into the neurobiological underpinnings of the relationship between genetic risk for obesity and maltreatment in MDD are provided by the presented fMRI results showing an interaction of polygenic risk for obesity and maltreatment on BOLD response of the right insula during reward processing. This finding again is in line with recent evidence from fMRI research suggesting hyperactivation in the insular cortex as a functional correlate of obesity (Batterink et al., 2010; Opel et al., 2015a). It however appears important to acknowledge that no main or interaction effects could be detected for BOLD response of the OFC in the present study. While our findings thus suggest that maltreatment and genetic risk for obesity associate with already established structural and functional correlates of obesity in reward related brain circuits, it appears that these structural and functional alterations are not directly overlapping but rather map onto differing anatomical structures. The observed lack of association between prefrontal brain structure and BOLD response during reward processing in the present study is in line with previous findings applying the same fMRI paradigm and contrast (Opel et al., 2015a) and might suggest that the investigated structural and functional correlates of obesity might develop independently.

Our findings might support the relevance of altered structure and function of reward related brain circuits in the development of obesity in MDD. This notion is even further supported by previous reports on associations between polygenic risk for obesity and OFC gray matter decrease in healthy subjects as well as by evidence from prospective MRI studies indicating an association between decreased prefrontal gray matter and weight gain during longitudinal follow up (Opel et al., 2017a, b; Yokum et al., 2012).

Most importantly, similar alterations in reward related brain circuits involving the OFC and the insula have previously been associated with major depression and are thought to play a key role in the development of affective disorders (Drevets, 2007; Engelmann et al., 2017; Kupfer et al., 2012; Price and Drevets, 2012; Redlich et al., 2015). Moreover, recent meta-analytic evidence of reduced OFC surface area in adolescent MDD patients might further highlight the potential role of OFC structural alterations as a shared biological correlate of obesity and MDD (Schmaal et al., 2017). The observed associations between PRS and altered reward processing in MDD patients moderated by early-life trauma could therefore mirror the frequently reported clinical association between depression and obesity (de Wit et al., 2010; Kloiber et al., 2007; Luppino et al., 2010; Opel et al., 2015b). Recent reports on associations between polygenic risk for obesity and atypical features of depression may support the notion of a partly overlapping neurobiological background of obesity and MDD (Milaneschi et al., 2017). However, the precise implications of the observed imaging correlates in the etiology of major depression depending on maltreatment status warrant further elucidation and replication in independent cohorts before firm conclusions can be drawn.

Limitations of our study comprise its cross-sectional design. Several studies proposed that depression could mediate the effect of early-life stress on obesity (Danese and Tan, 2014; Sacks et al., 2017). Yet, due the lack of longitudinal data, no firm conclusions can be drawn concerning this hypothesis. Moreover, the temporal pattern of the observed imaging effects remains uncertain. Even though our findings suggest that reward related structural and functional alterations are shaped by risk factors that clearly precede depression onset, the present data do not allow to infer on causal relationships and therefore the possibility that the observed imaging effects are influenced by depression or obesity itself cannot be completely suspended. In addition, while the applied fMRI contrast ("win > control") elicited BOLD response in a variety of widespread brain regions including the insula and the prefrontal cortex, it appears important to acknowledge that medial parts of the orbitofrontal cortex did not exhibit increased BOLD response during reward processing using this fMRI contrast. A further limitation might result from the fact that information on childhood maltreatment experiences and weight status were based on self report. However, the CTQ has been demonstrated to provide reliable results in several large imaging studies (Dannlowski et al., 2012; Frodl et al., 2017; Teicher et al., 2012) and retrospective and prospective assessments of childhood maltreatment have been shown to provide similar results regarding the increased risk of psychopathology (Scott et al., 2012). As another limitation the assessment of maltreatment experiences via the CTQ did not allow us to differentiate at which age adverse experiences occurred during childhood. Moreover, results from our previous work suggest that different types of BMI assessment (self reported vs directly measured weight and height) might not represent a major confounder in neuroimaging analyses (Opel et al., 2017a, b).

Strengths of the present study represent the inclusion of clinical, genetic and multimodal imaging data. The assessment of polygenic risk for obesity enabled us to study obesity related alterations in depressive phenotype in a cross-sectional design while excluding potential confounding by medication effects or effects of depressive symptomatology on the predictor variable. We additionally assessed medication load in all patients and controlled for its potential relevance in morphometric and fMRI analyses.

Another strength of the present study relies in the application of a multimodal imaging approach allowing us to directly confirm the relevance of altered reward processing in obesity and maltreatment on a morphometric and functional level.

5. Conclusion

To conclude, the present study provides evidence for the relevance of early-life trauma and polygenic risk for obesity on BMI as well as on brain structural and functional alterations closely related to reward processing in MDD. Our findings suggest that the influence of genetic load on BMI as well as on neurobiological correlates of obesity in MDD is moderated by childhood maltreatment experiences. Preventive measures targeting excessive weight gain in MDD patients should take into account the individual risk profile including both genetic predisposition as well as information on early environmental stress. Moreover, future studies should consider the potential influence and interplay of both genetic and environmental risk factors when investigating the neurobiological underpinnings of obesity.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.psyneuen.2018.09.027.

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