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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.