Larger amygdala volume in first-degree relatives of patients with major depression

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ABSTRACT

Objective: Although a heritable contribution to risk for major depressive disorder (MDD) has been established and neural alterations in patients have been identified through neuroimaging, it is unclear which brain abnormalities are related to genetic risk. Studies on brain structure of high-risk subjects – such as individuals carrying a familial liability for the development of MDD – can provide information on the potential usefulness of these measures as intermediate phenotypes of MDD.
Methods: 63 healthy first-degree relatives of patients with MDD and 63 healthy controls underwent structural magnetic resonance imaging. Regional gray matter volumes were analyzed via voxel-based morphometry (VBM).
Results: Whole-brain analysis revealed significantly larger gray matter volume in the bilateral amygdala in first-degree relatives of patients with MDD. Furthermore, relatives showed significantly larger gray matter volume in anatomical structures found relevant to MDD in previous literature, specifically in the bilateral hippocampus and amygdala as well as the left dorsolateral prefrontal cortex (DLPFC). Bilateral DLPFC volume correlated positively with the experience of negative affect.
Conclusions: Larger gray matter volume in healthy relatives of MDD patients point to a possible vulnerability mechanism in MDD etiology and therefore extend knowledge in the field of high-risk approaches in MDD.

1. Introduction

In recent years, research on neurobiological risk factors for major depressive disorder (MDD) has increasingly identified neurobiological contributions to disease risk. This is important since MDD is one of the leading causes of years lost due to disability (World Health Organization, 2009) and is associated with high mortality rates (Palazidou, 2012). One of the major methodological approaches in this domain has been neuroimaging. Several studies in patients reported functional as well as structural brain alterations (Drevets et al., 2008). Functional findings suggest dysregulation in neural circuits involving the prefrontal cortex as well as limbic structures (including the amygdala and hippocampus) (Price and Drevets, 2012). In line with these findings are results from structural imaging: Meta-analyses have highlighted volume reductions in the bilateral anterior cingulate cortex (ACC), dorsomedial frontal cortex, right middle frontal gyrus extending into the precentral gyrus, bilateral putamen, caudate, and right anterior insula/inferior frontal cortex in MDD (Bora et al., 2012). Arnone et al. (2012) described volume reductions in the frontal, orbitofrontal and cingulate cortices, hippocampus and striatum. Yet, as has been shown in a review by Frodl et al. (2008), some of these findings have been inconsistent, e.g., those concerning amygdala volumes. Diverging results might be due to methodological differences of study design and data analysis. Moreover, biological variables (e.g., age and sex) as well as psychopathological factors (e.g., age of onset, course of the disease and medication) might contribute to inconsistent findings (Arnone et al., 2012). Even given widespread and replicable structural–functional alterations in patients compared to controls, it remains unclear whether such changes occur after the manifestation of MDD symptoms, whether they represent risk factors for the development of MDD, or whether they are related to confounds such as comorbidity,

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medication use, social stress and lifestyle changes associated with having a severe mental illness.

Research on etiology of MDD has shown that multiple factors contribute to the manifestation of the disorder. MDD etiology is linked to interactions between genetic vulnerability – indexed not only by familial liability, but also by heritable traits such as neuroticism – and biographical/ environmental factors such as adverse life events (Burke et al., 2005). Often, risk factors are combined. For instance, patients with a family history of depression show a lower age of onset and are more likely to have recurrent depressive phases (Hollon et al., 2006). With an overall heritability of 30–40%, MDD is less strongly genetically determined than other severe mental illnesses, which emphasizes the importance of gene–environment interactions. One strategy to disentangle the complex network of influencing factors is to focus on high-risk subjects for MDD. Healthy first-degree relatives of MDD patients (H1stR) enable the investigation of vulnerability factors as well as resilience markers related to heritable or shared environmental (e.g., early familial) factors. While vulnerability factors are thought to increase risk of mental illness, resilience factors are considered to facilitate healthy functioning. Applied to quantitative, more biologically based measures such as neuroimaging, these studies add to the search for intermediate (or "endo"-) phenotypes. One necessary, but by no means sufficient, criterion for an endophenotype is that markers found in affected family members should also be found in nonaffected family members at a rate higher than that of the general population (Gottesman and Gould, 2003). Conversely, findings opposite in directionality between patients and their family members in similar systems may point to resilience factors protecting healthy relatives from manifest illness despite their genetic susceptibility. In the domain of brain structure, few manual tracing and voxel-based morphometry (VBM) studies searching for MDD endophenotypes have been published to date. Manual tracing studies revealed smaller hippocampal but larger amygdala volume in high-risk subjects (Boccardi et al., 2010; Rao et al., 2010; Saleh et al., 2012). The reduction in hippocampal volume in high-risk subjects compared to healthy controls or MDD patients was confirmed by VBM (Amico et al., 2011; Baaré et al., 2010; Carballedo et al., 2012; Chen et al., 2010; de Geus et al., 2007). Furthermore, VBM studies exhibited a reduction in local gray matter in the dorsolateral prefrontal cortex (DLPFC) (Amico et al., 2011; Carballedo et al., 2012). Nevertheless, the explanatory power of previous results regarding the potential structural endophenotypes of MDD is limited due to heterogeneity in sample sizes, studied risk populations and applied methods, e.g. region-of-interest (ROI) based analyses only.

To advance the data available in this field, we collected structural magnetic resonance imaging (MRI) data from a large sample of H1stR and matched healthy control subjects without any familial history of psychiatric illness (HC) and conducted a whole-brain VBM-analysis, thereby applying a very conservative statistical threshold. For consistency with the literature, we additionally tested our data for effects in regions previously observed using small volume alpha error adjustment. This approach decreases the probability of false positive as well as false negative findings and provides new insights in brain structural correlates linked to the genetic risk for MDD.

2. Methods and materials

2.1. Participants

All subjects were enrolled in a multicenter study (Esslinger et al., 2009) conducted by the Charité — Universitätsmedizin Berlin, the Universitätsklinikum Bonn and the Zentralinstitut für Seelische Gesundheit, Mannheim. The study was performed in accordance with the latest version of the Declaration of Helsinki and approved by the local Ethics Committees. Subjects participated in the study after providing written informed consent. 63 H1stR (38 females; 21 subjects from Berlin, 21 from Bonn and 21 from Mannheim) were measured and

63 HC (38 females; 21 subjects from Berlin, 21 from Bonn and 21 from Mannheim) matched for age and sex were taken from a larger study sample. Affected relatives of the H1stR group (43 offspring, 17 siblings, 1 parent, 2 NA) were examined by an experienced psychiatrist or clinical psychologist using the German version of the Structured Clinical Interview for DSM-IV (SCID-I) (First et al., 2002) or had to provide a medical report confirming a major depressive disorder. Both the H1stR and the HC group had no history of any neurological disorder or lifetime psychiatric axis I disorder including drug or alcohol dependence as verified by an interview according to the Screening Interview for DSM-IV axis I disorders. Further, subjects in the HC group were questioned carefully whether there is any knowledge about psychiatric disorders in their family, and special emphasis was put on first degree relatives. Subjects with axis 1 disorders or unclear diagnoses in their families were not included in the study sample. Handedness was measured by the Edinburgh Handedness Inventory (Oldfield, 1971) (H1stR: 55 right handers, 6 left handers, 2 both hander; HC: 57 right handers, 4 left handers, 2 both hander). In addition, years of education and premorbid intelligence assessed by the multiple choice verbal intelligence test (MWT-B) (Lehrl, 2005) as well as clinical scales such as the Symptom Check List (SCL-90-R) with the subscales Global Severity Index (SCL-GSI) and Depression (SCL-Depr) (Derogatis, 1983) were assessed. No significant difference between the two groups were found (see Table 1). Furthermore, a composite score (NegAff) comprising three self-report measures associated with the experience of negative affect was included, in detail: 1) the trait form of the Spielberger State/Trait Anxiety Inventory (STAI) (Spielberger, 1989) for the assessment of feelings of tension, fear and worry; 2) the neuroticism scale from the NEO five-factor inventory (Costa and McCrae, 1992) which assesses the degree to which an individual experiences negative affects such as anger, sadness and guilt; and 3) the harm avoidance scale of the Temperament and Character Inventory (TCI) (Cloninger, 1994) which measures a personality trait characterized by anticipatory worry, pessimism, easy fatigue and shyness. The composite score was calculated by using the average of the Z-scores for each individual scale as suggested previously (Holmes et al., 2012). The two groups did not differ on this scale either.

2.2. Statistical analysis of sociodemographical, psychometrical and clinical data

Statistical analyses were performed using the software package MATLAB (MATLAB 7.8, The MathWorks Inc., Natick, MA, 2009). Due to violation of statistical assumptions for parametrical testing (normal distribution as assessed by the Kolmogorov–Smirnov test or the level of measurement), the medians of age, years of education, IQ, SCL-GSI and SCL-Depr and the composite score NegAff were tested regarding group differences via non-parametrical Wilcoxon rank-sum test (see Supplementary Table S1).

2.3. MRI acquisition

Structural MRI data were acquired on a 3 Tesla Siemens MAGNETOM Tim Trio MRI system (Siemens, Erlangen, Germany) at all three study sites. All subjects underwent a T1-weighted three-dimensional magnetization prepared rapid gradient echo (MP-RAGE) sequence with an isotropic spatial resolution of 1 mm^3 (repetition time = 1.57 s, echo time = 2.74 ms, flip angle = 15°). Additional quality control measurements via EPI sequences were conducted at all study sites on every day of data collection according to a multicenter quality assurance protocol (Friedman and Glover, 2006), revealing stable signals over time and comparable quality between sites.

2.4. Voxel-based morphometry (VBM)

MRI data processing was performed according to an established voxel-based morphometry protocol using the VBM8 toolbox (Structural