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Cortical thickness and VBM in young women at risk for familial depression and their depressed mothers with positive family history

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ABSTRACT

It has been demonstrated that compared to low-risk subjects, high-risk subjects for depression have structural and functional alterations in their brain scans even before the disease onset. However, it is not known if these alterations are related to vulnerability to depression or epiphenomena. One way to resolve this ambiguity is to detect the structural alterations in the high-risk subjects and determine if the same alterations are present in the probands. In this study, we recruited 24 women with the diagnosis of Major Depressive Disorder (MDD) with recurrent episodes and their healthy daughters (the high-risk for familial depression group; HRFD). We compared structural brain scans of the patients and HRFG group with those of 24 age-matched healthy mothers and their healthy daughters at similar ages to the HRFD group; respectively. Both cortical gray matter (GM) volume and thickness analyses revealed that HRFD daughters and their MDD mothers had similar GM differences in two regions: the right temporoparietal region and the dorsomedial prefrontal cortex. These results suggested that the observed alterations may be related to trait clinical and neurophysiological characteristics of MDD and may present before the onset of illness.

1. Introduction

Major Depressive Disorder (MDD) is one the most common psychiatric diseases and it is predicted to become leading cause of disability in 2030 (WHO, 2004). Despite recent advances in the treatment of MDD, only half of patients with MDD achieve remission, and up to 20% of patients experience a chronic course of the illness (Steinert et al., 2014). Accumulated evidence suggests that different risk factors may play a dependent and independent role at different ages or time periods during the development of the illness. For example, recent stressful life events before the onset of the depressive episode are common in adulthood, whereas the presence of childhood trauma is commonly associated with the prognosis of the depression (Infurna et al., 2015; Kendler et al., 1999). Although there are sporadic cases, numerous studies have confirmed that MDD runs in families and this familial aggregation is likely to have both genetic and environmental (e.g., living with a depressed mother) components (Sullivan et al., 2000) (see Saveanu and Nemeroff (2012) for gene-environment interaction for depression). Epidemiological studies have shown that subjects with a history of familial depression have at least a two-to fourfold increased risk for MDD compared to people without family history (Gershon et al., 1982; Levinson, 2006). Depression risk further increases in females with positive family history, when compared to their male counterparts (Weissman et al., 2006). Once MDD has developed in the high-risk subjects, the course of the disease is more severe, recurrent, and treatment-resistant compared to sporadic cases (Gotlib et al., 2014). Therefore, it is essential to develop preventative options for the high-risk population. In order to create and implement these preventative options successfully, it is important to understand the

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etiology and pathophysiology of depression and identify the population who are at increased risk.

Research studies were successfully done in populations that are at high-risk for developing schizophrenia but they are at their infancy in bipolar and major depressive disorders. Many of these studies focused on identifying biological markers (also referred to interchangeably as endophenotype or intermediate phenotypes) related to the structural and functional alterations in the depressed brain (Hasler and Northoff, 2011; Hasler et al., 2004). Recent advances in technology and computer sciences are helping researchers to investigate the brain structures with more than one methodology, which help in identifying the biological markers better. Cortical volume and thickness measurements are two different methodologies that are used to evaluate the cortical brain structure (Fischl and Dale, 2000). Simply, cortical gray matter (GM) volume is defined, as the amount of GM that lies between the gray-white matter interface and pia mater. GM volume is a function of surface area and thickness of the measured area. On the other hand, cortical thickness is a measurement of the radial distance between the inner and outer border of cortical GM. Compared to volume analyses, thickness analyses are more sensitive to the columnar architecture of the cortex because it spans the cortical layers (Pakkenberg and Gundersen, 1997). Previous studies suggest that cortical surface area and thickness are independent from one another, both globally and regionally, and each of these measurements depend on different heritable factors (Panizzon et al., 2009; Winkler et al., 2010). Therefore, combining data obtained by different methodologies in order to investigate the GM would increase the quality of information obtained from a single MRI scan and allow for investigating of the GM alteration in study groups with complementary methods (Panizzon et al., 2009).

In MDD, regional structural alterations are well-defined in a large number of MRI studies, which mostly report altered GM volume both in the cortical and subcortical areas. Meta-analyses of these studies suggest GM reductions were noticeable in the basal ganglia, hippocampus, thalamus, orbitofrontal cortex (OFC), anterior cingulate cortex (ACC), frontal lobe, and gyrus rectus (Bora et al., 2012a; Kempton et al., 2011). In addition to region of interest studies, voxel-based morphometry studies, which are semi-automated whole-brain techniques, allow for regionally unbiased interrogation of differences in the brain tissue composition between groups, confirmed GM reductions in the anterior cingulate cortex, bilateral dorsomedial and right dorsolateral prefrontal cortices, and right anterior insula/inferior frontal cortex (Bora et al., 2012b). Nevertheless, GM volume studies were limited in populations that are at high-risk for developing depression. Some studies report reduced hippocampal volume in the healthy adolescent daughters of depressed mothers and in the adult relatives of depressed patients (Amico et al., 2011; Chen et al., 2010), while other researchers report increased amygdala volume in the relatives of patients with MDD (Rao et al., 2010; Romanczuk-Seiferth et al., 2014). The right dorsolateral prefrontal cortex (dlPFC) is another region that is found to have reduced GM volume in the healthy relatives of depressed patients (Amico et al., 2011). Contrastingly, Romanczuk-Seiferth et al. (2014) reported increased hippocampal and left dlPFC in the first-degree adult relatives of MDD patients. In a three-generation study, it was shown that the subjects at increased familial risk for MDD had widespread cortical thinning in the right hemisphere, specifically in the inferior parietal areas and frontal and temporal regions (Peterson et al., 2009).

Although some of the reported GM alterations were similar between the high-risk group and depressed patients, it is not clear if those alterations lead to vulnerability or if they are just epiphenomena. One way of clarifying it is to follow the high-risk groups and to detect the disease-associated changes, as subjects convert from high-risk status to developing MDD. Indeed, a recent study showed that during the development of depression, subjects with familial risk for mood disorders had reduced cortical thickness in the parahippocampal and fusiform gyrus, but had increased thickening in the left inferior frontal and precentral gyrus (Papmeyer et al., 2014). Another approach would be to detect the structural alterations in the patients and determine if the same alterations are present in high-risk subjects. In this study, we propose that common structural alterations in both patients and high-risk subjects would constitute trait markers while uncommon structural changes might be related to disease progress or treatment effect for patients. Based on this proposal, we recruited high-risk women with positive family history and their depressed mothers as probands. Our control group was composed of healthy mothers and their daughters to reduce the genetic variability across the control groups. We used two complementary, but different, approaches (i.e., voxel-based morphometry and cortical thickness measurements) to investigate the GM alterations in both MDD patients and their high-risk daughters for depression. Since it was previously reported that high-risk subjects have difficulty in regulating their emotions, we proposed that high-risk subjects would have GM alterations in frontolimbic regions, as these regions are known to play a key role in emotion regulation (Joormann et al., 2007; Price and Drevets, 2012). We also added the parietal cortex as a part of the region of interest because regional cortical thinning was previously reported in high-risk groups (Peterson et al., 2009).

2. Methods

2.1. Subjects

After the Ethics Committee of Ege University approved the study protocol, we recruited subjects via Internet advertisements and by invitation from the hospital database from 2009 to 2013. Among the initial screened 53 pairs of depressed mothers with their daughters, 24 women with the diagnosis of MDD with recurrent episodes (mean age: 46.2 ± 3.9 years) and their healthy daughters (the high-risk for familial depression group; HRFD) whose ages were between the ages of 18–26 (mean age: 22.3 ± 2.1 years) were included in the study (Table 1). An experienced clinical psychologist interviewed with the patients using a semi-structured questionnaire and reviewed all the medical records of the patients. The semi-structured questionnaire included the questions related to previous episodes and treatment. The questionnaire also consisted of explorative open-ended questions related childhood trauma modified from the Turkish Version of Childhood Trauma Questionnaire (Bernstein et al., 1997; Rezan, 2012). The recurrent MDD diagnosis was confirmed by using Structured Clinical Interview for DSM-IV (SCID) (Çorapçıoğlu et al.,1999; First et al., 1997). As this study aimed to study trait factors, we preferred MDD subjects without clinically significant depressive symptoms. However, due to the fact that many recurrent depressive patients have inter-episodic residual symptoms (Kennedy et al., 2004; Paykel, 2008), we allowed MDD mothers with mild symptoms, which were not leading to significant distress or functional impairments (Hamilton Depression Rating Scale (HAM-D) < 16 or Clinical Global Impression – Severity (CGI-S) < 4). The other inclusion criteria for the MDD mothers were 1) having no other axis I diagnoses including alcohol abuse, 2) having at least one healthy daughter between the ages 18–26 with no history of depression, 3) having at least one first-degree relative with an MDD diagnosis, 4) having no history of psychotic symptoms. Patients with unstable chronic medical illness (e.g. diabetes mellitus, hypertension, or chronic inflammatory disease) and those who had relatives with bipolar disorder or schizophrenia were excluded. The control group was composed of 24 age-matched healthy mothers (mean age: 47.3 ± 5.6 years) who had healthy daughters of similar ages to the HRFD group (mean age: 22.1 ± 2.1 years). The screening steps of the controls were identical to the patients with MDD and their daughters. The healthy daughters of the mothers in the control group constituted the low-risk for familial depression group (LRFD). Exclusion criteria for control groups were 1) any current or past psychiatric disorder confirmed with non-patient version of SCID interview (First et al., 2002), 2) having any first-degree relative diagnosed with major depression, bipolar disorder, or schizophrenia 3) having an unstable chronic medical illness, 4) having significant childhood trauma (e.g. sexual or physical abuse). All subjects that had been on steroid or similar treatments were excluded from all the study groups.

Mothers and daughters in the study gave their written informed consent after receiving a full explanation of the study's purpose and procedures. All the mothers in the MDD group continued their ongoing treatment without any modification for this study. All other subjects including the high-risk daughters were free of any