

Small Frontal Gray Matter Volume in First-Episode Depression Patients

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Abstract

Objective: Brain imaging studies have shown that depressed individuals suffer from inadequate frontal lobe functions vis à vis smaller frontal lobes. The effects of depression's recurrent nature and long-term antidepressant treatment are not definitely known. This study aimed to examine frontal lobe volume at the onset of clinical depression by including first-episode drug-naïve depressed patients.

Method: The study included 23 first-episode drug-free major depression patients diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) and 28 healthy age- and sex-matched controls. Cranial magnetic resonance (MR) images were obtained in both groups using a 1.5 Tesla device. Gray and white matter volumes in the frontal lobes were measured using the Medical Image Processing Analysis and Visualization (MIPAV) computer program.

Results: Frontal gray matter volume in the patients was lower than that in the control group. White matter and total intracranial volume did not differ between the 2 groups. Small gray matter volume was not correlated with the duration or severity of illness.

Conclusion: The results of this study indicate that frontal lobe gray matter volume is low in first-episode depressed patients and is independent of both illness severity and duration. This result suggests that the observed changes in the frontal lobe could have occurred before the clinical symptoms of depression were observed.

Key Words: Depression, cerebral cortex, frontal lobe, MRI.

INTRODUCTION

According to the World Health Organization (WHO), unless novel preventative and treatment options are found major depressive disorder (MDD) will be the second most common cause of work loss by 2020 (WHO, 2001). Although depression is a common disease, its etiology is not fully known. Clustering of the illness within families implies there are genetic factors at play; however, research has not shown that there is a single causative gene and it is proposed that many genes are involved in the illness (Levinson, 2006). Additionally, early life trauma and stressful events that occur within 12 months of its onset have been shown to play a role (Goodyer and Altham, 1991; Caspi et al., 2003).

Recently, it has been suggested that genetic and environmental factors may interact, resulting in the illness (Charney and Manji, 2004; Monroe and Reid, 2008). The gene-environment interaction begins in the first year of life; however, MDD usually occurs during early adulthood. As such, the process that occurs before clinical symptoms appear is of significant importance.

MDD studies regarding brain lesions, and brain structure and function show that the limbic, cortical, striatal, pallidal, and thalamic neural circuits may play a role in the illness (Drevets et al., 2008; Koolschijn et al., 2009); the frontal lobe and the limbic system are the most strongly associated regions. Yet, it is not clearly known whether the reported results are present before the onset of illness or if

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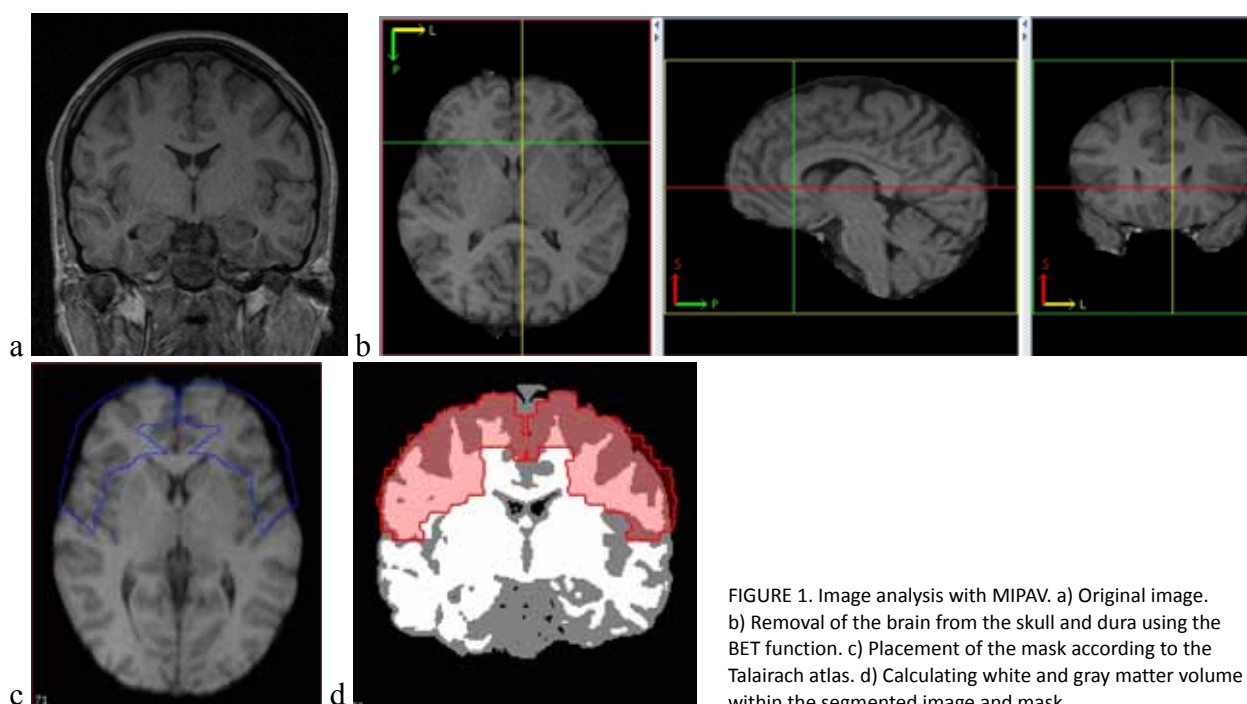


FIGURE 1. Image analysis with MIPAV. a) Original image. b) Removal of the brain from the skull and dura using the BET function. c) Placement of the mask according to the Talairach atlas. d) Calculating white and gray matter volume within the segmented image and mask.

the repetitive nature of the illness and drug use affect the reported results (Monkul and Ozerdem, 2003).

Two different approaches may be adopted in the study of MDD. The first suggests that high-risk individuals may be chosen as the study group and, if appropriate, they must be followed-up. Such studies show that individuals that carry a genetic risk exhibit functional or structural changes, especially in the hippocampus and right frontal cortex (Gatt et al., 2009; Peterson et al., 2009). The primary limitation of this approach is that a large proportion of at-risk individuals are not diagnosed; therefore, to what extent the previous reported results are related to the patients' clinical status is questionable. The other approach is to form a study group with first-episode depression patients. In this way it is possible to minimize the effect of iterative episodes and drug use. Studies on first-episode MDD patients are limited in number and the results of these studies indicate that the volume of the anterior cingulate (an extension of the limbic system), hippocampus, and orbitofrontal cortex may be smaller in depressive patients (Tang et al., 2007; Kaymak et al., 2009; Zhang et al., 2009). Hippocampal findings in first-episode depression are discussed elsewhere (Eker and Gonul, 2009).

Studying first-episode and drug-naïve depressive patients, the hypothesis that frontal lobe volume differences are present at disease onset can be tested. The frontal lobe is a region of interest because it appears to

be an important part of the limbic-cortical-striatal-pallidal-thalamic neural circuits and it exhibits remarkable pathology in many structural studies (Drevets, 2007; Drevets et al., 2008). The frontal lobe consists of many functional regions, but there is no consensus concerning the boundaries of these regions. As such, whole frontal lobe volume is measured without any discrimination.

METHODS

Study sample

The study included 23 right-handed patients that were referred to the Ege University Psychiatry Outpatient Unit and met the criteria for MDD according to the Diagnostic and Statistical Manual of Mental Disorders-IV Text Revision (DSM-IV TR) criteria. Each patient was re-examined by a psychiatry specialist after an initial outpatient assessment. Then, they were informed about the study and after providing written informed consent a senior psychiatry resident blind to the diagnosis administered the Structured Clinical Interview for DSM-IV (SCID) (First et al., 2001).

Inclusion and exclusion criteria

The first criterion was diagnosis of the first episode of MDD and that the patients had no other Axis I disorder. The control group was formed of 28 right-handed age- and gender-matched volunteers without an Axis

TABLE 1. Sociodemographic features of the patient and control groups.

	Depression Group (n = 23)	Control Group (n = 28)	Comparison
	Mean $\pm$ SD	Mean $\pm$ SD	
Age (years)	30.4 $\pm$ 8.9	31.4 $\pm$ 7.4	t = 0.45, df = 49, P > 0.05
Gender (M/F)	5/18	11/17	χ^2 = 1.80, df = 1, P > 0.05
Duration of illness (weeks)	48 $\pm$ 49.3	-----	
Age of onset	28.4 $\pm$ 7.75	-----	
Hamilton Depression Rating Scale Score	25.5 $\pm$ 4.7	-----	
Frontal Gray Matter (cm ³)			
Right	129.73 $\pm$ 20.17	140.12 $\pm$ 20.43	t = 1.81, df = 49, P = 0.07
Left	123.98 $\pm$ 17.38	138.62 $\pm$ 24.89	t = 2.38 df = 49 p = 0.021*
Frontal White Matter (cm ³)			
Right	77.2 $\pm$ 32.04	70.37 $\pm$ 26.46	t = 0.83, df = 49, P > 0.05
Left	81.65 $\pm$ 31.41	73.2 $\pm$ 27.24	t = 1.02, df = 49, P > 0.05
Total Cranial Volume (cm ³)	1456.5 $\pm$ 160.8	1489.7 $\pm$ 143	t = 0.8, df = 49, P > 0.05

*P values <0.025 are statistically significant because the 2 hemispheres were measured separately.

I disorder. To increase the homogeneity of the patient and control groups, those with a history of bipolar or psychotic disorder (schizophrenia, delusional disorder, schizoaffective disorder) in their first-degree relatives were excluded. Those with a history of chronic systemic illness and head injury resulting in loss of consciousness, and individuals with antisocial personal traits detected by physical examination and laboratory results were also excluded.

In all, 18 of the patients included in the study had never taken antidepressants. The remaining 5 had not used any psychotropic medication within the least 20 days; however, medical records indicated intermittent and short-term use of antidepressants (mean: 4 $\pm$ 8 weeks). The Hamilton Depression Rating Scale (Hamilton, 1960) was administered to the patients to assess the severity of depression on the same day with MR scan. After the MR scan treatments for depression were determined for the patients. During the follow-up period 86% of the patients (20/23) responded to either the first or second antidepressant given.

MATERIALS

SCID is a diagnostic scale that was developed by First et al. (1997). Validity and reliability of Turkish version were conducted by Ozkurkcuoglu et al. (1999). The Hamilton Depression Rating Scale (a structured interview) was used to assess the severity of depressive symptoms. The validity and reliability of the Turkish version were conducted by Aydemir et al. (2006).

MR scans of the patients were made using a 1.5 T Siemens MR device. Images were later analyzed using

the Medical Image Processing Analysis and Visualization (MIPAV) computer program (Figure 1). The coordinates for the anterior commissure were maintained by a program before analysis and this point was considered as '0' for the x, y, and z coordinates. Analysis included removal of the skull, segmentation, and maintenance of the Talairach transformation matrix, respectively. After normalization of the segmented images according to the Talairach atlas, the borders of the frontal lobe were obtained by applying the atlas to the image (Talairach and Tournoux, 1988). After the determining the borders, the images were multiplied by the inverse Talairach transformation matrix and measurements were obtained. The frontal lobe forms approximately 1/3 of the brain's cortical tissue, beginning at the central sulcus. The postero-lateral boundary is drawn by the lateral sulcus. The ventral neighbors are the orbital region of the head base and the posterior boundary is drawn by the cingulate sulcus. Total brain volume is calculated as overall gray matter, white matter, and cerebrospinal fluid (CSF) that fill the sulci.

Statistical analysis

Sociodemographic data for the patient and control groups were compared by t and chi square tests. Frontal lobe volume in each hemisphere was measured separately and compared by t test. Because the groups were matched for age and gender, no further testing of these confounding variables was required. The asymmetry index was calculated as follows: $\{2 \times (\text{right-left})/(\text{right} + \text{left}) \times 100\}$. The relationship between clinical data and frontal lobe data was examined by Pearson's correlation coefficient. In comparing frontal lobes, because the right

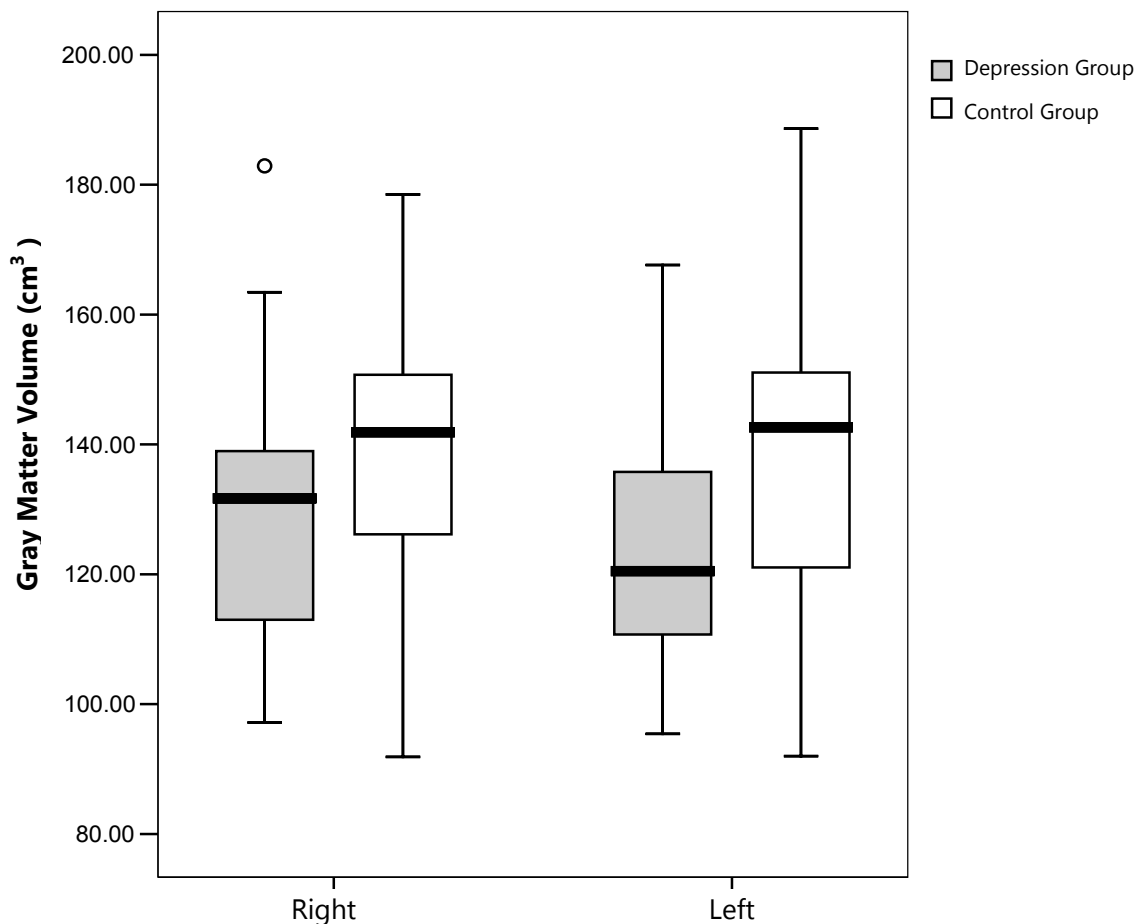


FIGURE 2. Frontal lobe gray matter differences between the patient and control groups (statistical assessment is presented in Table 1).

and left were evaluated separately, a P value <0.025 was considered significant, while for linkage analysis P values <0.05 were considered significant.

RESULTS

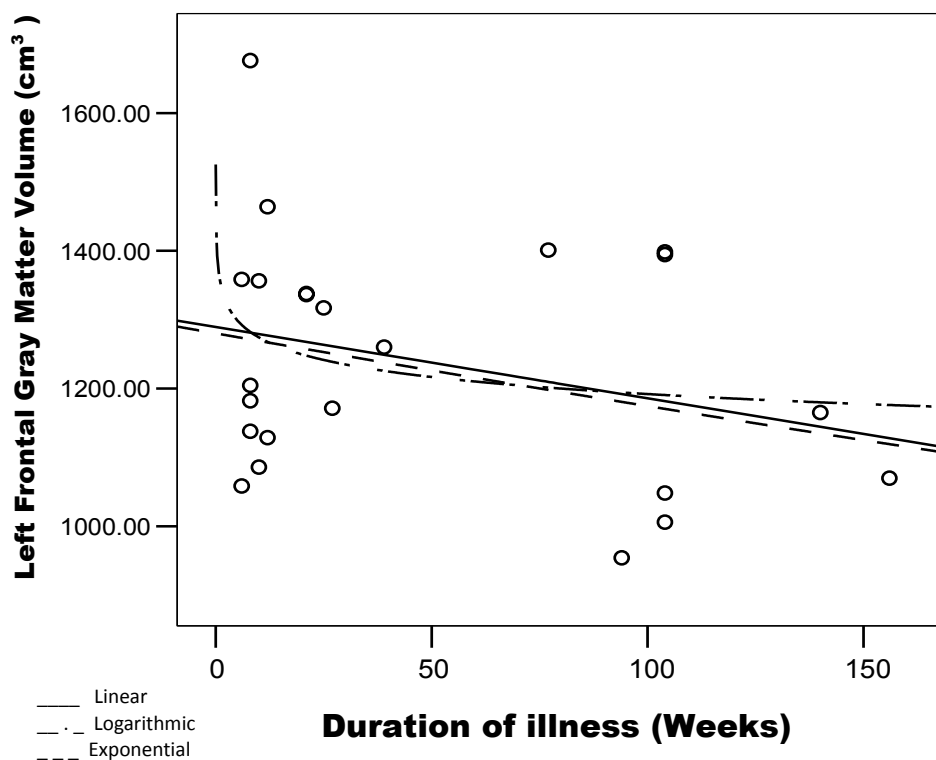
There weren't any differences between the patients and controls regarding age or gender (Table 1). Following the psychiatric evaluation in 2 patients, a history of childhood physical and sexual abuse was determined.

Comparison of frontal lobe volume in patient and the control groups

Differences in frontal lobe gray and white matter volume between the patient and the control groups were evaluated separately. Left frontal lobe gray matter volume was significantly lower in the patient group ($t = 2.38$, $df = 49$, and $P = 0.021$; Cohen $d = 0.68$) (Table 1, Figure 2) and right frontal lobe gray matter volume was also lower in the patient group, although the difference

TABLE 2. The correlation matrix for frontal lobe volume and clinical variables.

	Right frontal gray matter	Left frontal gray matter	Right frontal white matter	Left frontal white matter
Hamilton Score	$r = -0.139$ $P = 0.528$	$r = -0.035$ $P = 0.873$	$r = 0.116$ $P = 0.599$	$r = 0.042$ $P = 0.849$
Age of illness onset	$r = 0.021$ $P = 0.923$	$r = -0.119$ $P = 0.588$	$r = 0.184$ $P = 0.400$	$r = 0.157$ $P = 0.475$
Duration of illness (weeks)	$r = -0.133$ $P = 0.545$	$r = -0.294$ $P = 0.174$	$r = -0.079$ $P = 0.721$	$r = -0.025$ $P = 0.909$



	Model Summary					Parameter Approximates	
	R ²	F	df1	df2	Sig.	Constant	b1
Linear	.086	1.984	1	21	.174	1289.434	-1.035
Logarithmic	.057	1.271	1	21	.272	1356.592	-35.739
Exponential	.094	2.176	1	21	.155	1280.159	-.001

FIGURE 3. Analysis of the relationship between the duration of illness and left frontal lobe gray matter volume.

was not statistically significant ($t = 1.81$, $df = 49$, and $P = 0.07$; Cohen $d = 0.51$). One patient was observed to have right frontal lobe gray matter volume 2 standard deviations greater than the patient group mean. When this patient was removed from the analysis right frontal lobe gray matter volume was significantly lower in the patient group than in the control group and the effect size was same as for the left side ($t = 2.36$, $df = 48$, and $P = 0.022$; Cohen $d = 0.68$) (Figure 2). White matter volume in the 2 hemispheres did not differ (right: $t = 0.83$, $df = 49$, and $P > 0.05$; left: $t = 1.02$, $df = 49$, and $P > 0.05$). The white and gray matter asymmetry index in the patient and control groups did not differ ($P < 0.05$).

Linkage analyses between frontal lobe volume and clinical variables

A significant relationship was not observed between

frontal lobe gray matter and white matter volume, and the clinical variables (age, age of onset of illness, duration of illness, and HAD score), based on linkage analysis (Table 2). As such, logarithmic and exponential relationships were tested, as well as the linear relationships, but statistically significant differences were not observed (Figure 3).

Duration of illness was more than one year in 8 of the patients (34%). The collection of data regarding the log10 base in order to reduce high variance in duration of illness also did not change the linkage results. When patients that reported that they were depressed for more than one year were separately clustered and analyzed via a different method, no differences were observed in the linkage results (duration of illness more than one year: right gray matter: $r = 0.021$ and $P > 0.05$; left gray matter: $r = 0.043$ and $P > 0.05$; duration of illness less than

one year: right gray matter: $r = -0.09$ and $P > 0.05$; left gray matter: $r = -0.29$ and $P > 0.05$). Similarly, no difference in gray matter was observed when patients were grouped according their illness duration (more than one year vs less than one year) (Mann Whitney test for right: $U = 54$ and $P > 0.05$; for left: $U = 44$ and $P > 0.05$).

DISCUSSION

The data obtained in the present study show that the first-episode depression patients had less frontal gray matter than the control group; this result was noted in both hemispheres. No difference between groups was detected in white matter volume. No relationship was observed between the duration of illness or severity of illness, and gray and white matter volume. The majority of the patients had never taken any medication before the study and the remainder used drugs for a very short time or were drug naive when the study was conducted; therefore, we propose that the results are independent of the effects of drugs.

In recent years 2 contemporary hypotheses that may explain the etiology of depressive disorder have been tested. The first of these is that the hypothalamopituitary axis functions above the normal average level and that high glucocorticoid levels may damage neural circuits in the brain (Pariante, 2006). The other is that there is impairment in neural plasticity and neurogenesis (Schmidt and Duman, 2007). The main molecules cited in the second hypothesis are serotonin and brain-derived neurotrophic factor. Malfunction of the systems mentioned in both hypotheses are thought to damage brain function and structure. One of the main steps in testing these hypotheses is to measure the damage. Improvements in MR techniques allow the structure of the brain to be explored at the millimetric level. Many imaging studies conducted with these techniques compared limbic and frontal structure volumes in patients and healthy controls. The hippocampus is the main region studied because it is considered the most affected nucleus (Eker and Gonul, 2009). This nucleus is one of the structures most vulnerable to negative conditions like hypoxia and high glucocorticoid levels (due to its high number of receptors). It is also responsible for some of the cognitive functions that are observed to be impaired (Kaymak et al., 2009). Other than the hippocampus, the glucocorticoid receptors in the brain are primarily located in the frontal cortical structures (Patel et al., 2000). In a study that reviewed MR studies conducted with depression patients, Koolschjin et al. (2008, 2009) reported that the decrease observed in the prefrontal, anterior cingulate,

and orbitofrontal cortex is more than that in the hippocampus. This finding shows that the frontal lobe structures and cingulate cortex may play a role, along with the hippocampus, in the pathophysiology of depression.

The boundaries between the prefrontal cortex that form the frontal lobe and premotor/motor cortex have been examined in anatomical studies, but because of individual differences there has not been a consensus regarding the limitations of these regions (Rademacher et al., 1993; Crespo- Facorro et al., 1999; Ramnani and Owen, 2004; Nachev et al., 2008; Nachev et al., 2009). Other regions of interest in the frontal cortex are the orbitofrontal cortex and medial prefrontal cortex. These two regions are difficult to differentiate into functional and anatomical boundary regions (Crespo- Facorro et al., 1999). As such, rather than measuring the regions with controversial boundaries and without clear functional segregations, the approach that measures a single combined region of interest (frontal lobe) is adopted. The second reason for combining these regions is that they cause the clinical symptoms seen in depression that are closely related to each other (action, attributions, cognitive functions, anhedonia, and impulsivity) (Drevets, 2007; Drevets et al., 2008). The literature contains only 1 study that measured the entire frontal lobe. In this study the frontal lobe in depression patients was reported to be 7.2% smaller than in healthy controls (Coffey et al., 1993). Although the results of our study (approximately an 8.6% decrease) are similar, mean age in our patient and control groups was lower. Depression patients included in a study by Coffey et al. (1993) were non-responsive to treatment, although they had been on pharmacological treatment for many weeks and were referred for electroconvulsive therapy. The reoccurrence of this finding in patients that were younger and non-resistant to treatment suggests that volumetric changes are independent of the duration of illness, which will be discussed in detail later. Another difference between the studies is the methods of measurement. Coffey et al. (1993) did not perform segmentation; therefore, the differences in white and gray matter volume were not effectively assessed.

Although decreases in the orbitofrontal and anterior frontal regions are thought to be frequent in older patients, similar findings have been reported in young adult populations (Lai et al., 2000; Taylor et al., 2003; Ballmaier et al., 2004; Koolschjin et al., 2009). In a study conducted with elderly patients, orbitofrontal atrophy was not associated with cerebrospinal fluid volume. This might be due to small orbitofrontal lobe was developmental and

and may have been independent of the duration of illness (Ballmaier et al., 2004). Peterson et al. (2009) followed individuals at high risk for depression for 3 generations and observed a decrease in cortical thickness, especially in the right frontal regions. Although there were depressed individuals in the risk group, the findings were mainly related to the risk, rather than a diagnosis of depression. Among lesion studies, one of the most frequent findings is that stroke in the left frontal lobe causes depression (Narushima et al., 2003; Drevets et al., 2008). When the effect of left frontal lobe structures on the limbic system and hypothalamus functions are taken into account, injuries on the left side are suggested to induce depression (Narushima et al., 2003; Drevets et al., 2008).

When the data above are considered, the low right frontal lobe volume observed in the present study might have been related to genetic load and/or might be an endophenotypic marker. The difference we observed in the left hemisphere is consistent with the results of lesion studies and studies that reported a decrease in gray matter (Drevets et al., 2008). Additionally, it may be suggested that the differences observed in both regions were not limited to the process in which symptoms are evident, as our findings are not related to the duration of illness. We want to highlight some limitations concerning the duration of illness and the interpretation of the relationship analysis. First, duration of illnesses in the patients in the present study was self-reported; self-reports should always be considered potentially inaccurate. A wide variance of illness duration was obtained when we included depressed patients with illness history of only few weeks and patients with a history of more than one year. This variance might benefit linkage calculations, but it may also negatively affect the group's homogeneity. The patients did not use any medications because they did not consider that their symptoms were due to a psychiatric disorder. By taking into account that self-reported duration of illness might have been inaccurate, patients that reported they were depressed for more than one year were excluded, but no differences were observed in the results of the linkage analysis. Another issue for the volume measurement studies is including treatment resistant patients who might have smaller volumes compared to non-resistant patients in the study group (Frodl et al., 2008). This thought is not supposed to be valid for our study, because our patients had a rate of response over 80% regarding to their first or the second antidepressant treatment during follow up.

Post mortem studies on depressive patients have reported a decrease in the number of neutrophils in the

frontal regions, although no signs of neuron death have been observed (Cotter et al. 2001). Glial cell loss accompanies neuron atrophy (Cotter et al., 2002). The observed cellular changes are suggested to be related to increased cortisol levels or a decrease in neurotrophic factors (Cerqueira et al., 2005). The genes that code glucocorticoid receptors exhibit functional changes under the influence of environmental factors, and these changes have been proven to affect such brain structures as the hippocampus (Zobel et al., 2008; McGowan et al., 2009). Regarding the effect of increased cortisol levels on the brain, it is reported that the hippocampus is affected to a greater degree in the early childhood of neurodevelopment and the most vulnerable time for the frontal lobe is adolescence, as it is the period during which most changes take place (Pruessner et al., 2009). The current literature indicates that cortisol level increase in adolescents that don't clinically present with depression, but are at risk due to family history (Goodyer, 2008; Rao et al., 2009). This finding is consistent with the theory that damage in the frontal lobe occurs during adolescence. Another finding of the present study that supports this theory attributing the changes to adolescence is that total brain volume did not differ between the groups (Table 1). The skull and brain reaches 90% of adult volume by the end of the sixth year of life (Giedd et al., 2006); there is very limited growth afterwards. Frontal cortical thickening reaches its highest level between 11 and 13 years of age (Giedd et al., 2006). In the normal physiological process, frontal gray matter begins to decrease after this time. As such, it can be suggested that gray matter decreases in the first-episode depressive patients was related to high cortisol levels during adolescence, when the frontal lobe were most vulnerable to change. This is related more to the pre-clinical presentation than to the syndromal beginning of clinical symptoms. It can also be stated that the clear loss of gray matter during the vulnerable state continues, though not to as high a degree, and may result in the clinical presentation of depression. The above explained, may account for the finding of this study stating no linear relationship between the period of the disorder and the loss of gray matter. Nevertheless, the data of this study are not adequate to test this cortisol suggestion directly.

Two of the patients in our patient group had experienced childhood trauma. Although some researchers suggest that a history of trauma in depressive patients is common, it is also known that there is high comorbidity of psychiatric disorders in people with a history of trauma. Due to our inclusion criteria, which did not allow

us to take people with comorbidity, the trauma group may have been excluded from the study. The presence of a history of trauma in only 2 patients suggests that our findings are independent of childhood trauma.

In the MR studies those have used diffusion methods which have been developed to indicate the white matter pathologies, it has been reported that there could be a pathology in the white matter of the depressive patients (Li et al. 2007, Ma et al. 2007). Our findings are not consistent with these findings. The technique used in the present study was developed for gray matter measurement. Thus, it is less reliable and sensitive for the measurement of white matter and we therefore don't suggest that our findings regarding white matter are as reliable as those concerning gray matter. Another reason for not

finding any difference is the fact that white matter may be more related to the total duration of the disorder and in our first episode patients, these white matter pathologies may not yet have developed.

In conclusion, frontal lobe gray matter volume observed in the first-episode depressive patients was lower than in the controls, and was independent of the duration of illness. The present study's findings show that the frontal lobe was affected by the development of depression, similar to the frontal cingulate cortex and hippocampus, which are reported to be small in depressive patients. For the development of a theory about the etiology of depression, it is suggested that the findings of the present study should be examined and future studies on changes in the frontal lobe are warranted.

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