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RESEARCH ARTICLE

Is it important to take the co-occurrence of obesity and cigarette smoking into account in brain imaging studies in major depressive disorder?

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ABSTRACT

Objective: To date, a small number of studies have investigated cortical thickness, cortical surface area, and subcortical volume abnormalities in first-episode, untreated patients with Major Depressive Disorder (MDD). The findings of previous studies are not entirely consistent. Previous studies did not match first-episode, untreated patients with MDD to controls regarding body mass index (BMI) and smoking, which could contribute to the inconsistency of results. The aim of the current study was to examine whether morphological abnormalities are present in first-episode and untreated MDD patients in comparison with well-matched controls, particularly concerning BMI and smoking status.

Method: Twenty first-episode, untreated patients with MDD were enrolled in the study along with 20 healthy controls (HC) matched for age, education, sex, BMI and smoking status. Thickness and area of the cortex and subcortical volumes were measured using surface-based morphometry implemented with Freesurfer (v5.3.0).

Results: There were no significant differences in cortical thickness, surface area, and subcortical volumes between the first-episode, untreated patients with MDD and HC groups.

Conclusion: This study provides evidence that cortical thickness, cortical surface area, and subcortical volumes might be normal in first-episode untreated patients with MDD in comparison with well-matched controls, particularly for BMI and smoking status.

Keywords: Cortical thickness, major depressive disorder, structural imaging, subcortical volume

INTRODUCTION

Major Depressive Disorder (MDD) is one of the most common mental disorders and is a leading cause of disease burden worldwide (1). Nevertheless, despite the increasing prevalence and disease burden of MDD, the neurobiological mechanisms underlying the disorder remain unclear.

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Recent neurobiological models suggest that impaired neuroplasticity and neurogenesis due to alterations in neurotrophic factors, increased glucocorticoid exposure or chronic inflammation play a prominent etiologic role in depression (2). Therefore, neuroimaging studies can provide important insight into the neurobiology of MDD. Available evidence suggests that MDD might be associated with overall reductions in regional subcortical and cortical volume (3-9) and abnormalities in cortical thickness and surface area (10). However, the effect sizes of these changes are small to modest and there is a considerable heterogeneity across studies. For example, some surface-based morphometry (SBM) studies have found increased cortical thickness (11,12), whereas others reported lower (10,13-15) or similar (16,17) cortical thickness in patients with MDD compared to healthy controls. These inconsistent findings might be at least partly attributed to the effects of medication (8) or the influence of chronic or recurrent episodes (18). Therefore, first-episode studies in unmedicated patients with MDD are important to reveal structural brain findings that are not confounded by either potential neurotoxic effects of prolonged stress and recurrent episodes or neuroprotective effects of antidepressant medications.

To date, a small number of SBM studies have investigated cortical thickness abnormalities in first-episode, untreated patients with MDD. Unlike the findings of most of the studies in recurrent MDD, a number of them found increased (11,12,19) or both increased and decreased (20,21) cortical thickness in first-episode, untreated patients with MDD compared to controls. However, a few other studies reported decreased (22,23) or preserved (24) cortical thickness in this patient group. Similar to cortical thickness studies, the findings of previous studies that examined subcortical volume alterations in various regions in first-episode, unmedicated MDD (mostly hippocampus and amygdala) are not entirely consistent. Meta-analyses observed smaller hippocampal and amygdala volumes in patients with first-episode MDD (7,25). However, recent studies reported no difference in hippocampus and amygdala volumes (22,24,26) and in other subcortical structures in (22,24,27) in first-episode patients with MDD.

There are a number of potential factors that can contribute to inconsistent findings across studies in MDD. While some factors such as illicit drug use and history of significant co-morbid medical disorders are frequently excluded in brain imaging studies in MDD, the effects of obesity and cigarette smoking on cortical and subcortical changes have been generally neglected. Obesity is associated with depression even in early stages of life (28). Chronic stress leads to resistance to leptin receptors, contributing to obesity (29). Both active and passive smoking often leads to respiratory symptoms (30). Respiratory symptoms, obesity, and depression are mediated by proinflammatory cytokines (31) and neuropeptide Y (32). Obesity and cigarette smoking are more prevalent among patients with MDD compared to the general population (33,34) and are reported to alter the structural changes in MDD patients (35,36). Moreover, obesity and smoking also modify subcortical volumes (36-38). It is therefore of importance to take the co-occurrence of obesity and cigarette smoking into account in brain imaging studies in MDD. However, no previous studies matched first-episode, untreated patients with MDD to controls on body mass index (BMI) and smoking, which could contribute to the inconsistency of results.

Our hypothesis is that smoking status and obesity are important confounding factors that should be considered in imaging studies in untreated first-episode depression patients. The aim of the current study was to examine whether morphological abnormalities are present in first-episode and untreated MDD patients, in comparison with well-matched controls, particularly for BMI and smoking status.

METHOD

Twenty first-episode, untreated patients with MDD were enrolled in the study along with 20 healthy controls (HC). All MDD patients were diagnosed using the Structured Clinical Interview for DSM-IV (SCID-I) (39) and met the following inclusion criteria: fulfilling DSM-IV criteria for major depressive disorder; aged 18-65; no comorbid Axis I psychiatric disorders, including anxiety disorders; currently experiencing an episode of depression with a score of at least 20 (indicating at least moderate severity) on the 17-item Hamilton Depression Rating Scale (HDRS-17) (40). The healthy group consisted of individuals with no current or past Axis I disorder as assessed by the SCID.

Exclusion criteria for all participants included: <18 years of age; any MRI contraindications; pregnancy; history of head injury or neurological disorder; abuse of or dependence on alcohol or other substances; any family history of bipolar or psychotic disorder in their first-degree relatives and any concomitant medical disorder.

MDD patients and control subjects were matched for sex, age, years of education, handedness (all were right handed), smoking status, and BMI. Non-smoker

MDD patients as well as HCs had no smoking history. Smoking severity was assessed with the Fagerström Test for Nicotine Dependence (FTND) (41). BMI was determined as weight in kilograms divided by height squared in meters. All participants underwent baseline clinical assessment and an MRI scan within 48 hrs of initial contact.

All participants gave written informed consent to participate in the study. This study was approved by the local research and ethics committee.

Measures

Hamilton Depression Rating Scale (HDRS-17): This scale, which measures the level and severity of the patient's depression, was developed by Hamilton (40). This scale has been validated for Turkish society (41).

Fagerström Test for Nicotine Dependence (FTND): This test was developed by Karl O. Fagerström (42) in order to determine the level of physical dependence on smoking and consists of six items. As the level of addiction to smoking rises, the score from the test increases. The validity and reliability study of the test in the Turkish language was performed by Uysal et al. (43).

MRI Acquisition

All MRI scans were performed on a 1.5 T Achieva MR imager (Philips Medical Systems, Eindhoven, Netherlands) with a standard quadrature head coil. All subjects were scanned with a 3D T1-weighted turbo gradient echo sequence with SENSE using the following parameters: coronal orientation, matrix 256x256, 1x1 mm^2 in-plane resolution, slice thickness 1 mm, TE/TR=5.6/12 ms, flip angle α=19°. All scans were inspected to check for motion artifacts and to rule out gross neuropathology.

Cortical Thickness and Surface Area Analysis

T1 images were analyzed using the FreeSurfer software package (version 5.3.0, http://surfer.nmr.mgh.harvard.edu), which is freely available online. Imaging processing procedures were based on previous reports (44,45). Briefly, processing steps included motion correction, removal of non-brain tissue, transformation to Talairach-like space, segmentation of subcortical gray/white matter tissue, intensity normalization, tessellation of the gray matter-white matter boundary, automated topology correction, and surface deformation. Cortical surfaces then underwent inflation, registration to a spherical atlas, and automatic identification of gyral and sulcal regions. Cortical thickness was measured by averaging the distance between the pial surface and grey-white surface. Surface area for each vertex was calculated as the average of the surrounding triangles (46).

Based on previous studies (10,47), we selected the bilateral fusiform gyrus, rostral anterior cingulate cortex, insula, medial orbitofrontal cortex, rostral middle frontal cortex, and superior temporal cortex as regions of interests (ROIs) for additional analysis of cortical thickness.

Subcortical Volume Analysis

Left and right hippocampus, amygdala, thalamus, caudate, putamen, pallidum and nucleus accumbens volumes and intracranial volume (ICV) were calculated by the automated procedure for volumetric measures of brain structures implemented in FreeSurfer for further statistical analysis.

Statistical Analysis

Cortical thickness and area maps were smoothed with a full-width half-maximum Gaussian kernel of 15 mm to ensure a well-powered cross-sectional cortical thickness study because of our modest sample size (48). FreeSurfer's Query, Design, Estimate, Contrast (QDEC) tool was used to test for cortical thickness and surface area differences between MDD and healthy controls. A general linear model was used to identify between-group differences in thickness and area estimates with age and sex as covariates of no interest. We used an uncorrected threshold of $p<0.05$ for initial vertex-wise comparisons. Thereafter, multiple comparisons were corrected with a Monte Carlo Simulation using a threshold of 1.3 ($p<0.05$). All analyses were performed for the right and left hemispheres separately.

The 14 subcortical structure volumes and ICV were imported into SPSS 16.0 for statistical analyses. A GLM was used to analyze subcortical volume differences between groups, with sex as categorical predictor and age and ICV as continuous predictors.

Demographic and clinical characteristics were assessed for the normality of their distribution using Kolmogorov-Smirnov normality test. Parametric and non-parametric tests were used as appropriate. For all analyses, the level of significance was $p<0.05$. Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS, v16.0).

RESULTS

Clinical and demographic characteristics of the sample are described in Table 1. There were no significant

differences between the groups in age, sex, BMI, smoking status, or years of education.

There were no significant differences in cortical thickness and surface area between the first-episode, untreated patients with MDD and HC groups. There were also no significant differences in mean cortical thickness values of cortical ROIs between groups (Table 2).

There were no significant differences in subcortical volumes between the first-episode, untreated patients with MDD and HC groups at a significance level of $p<0.05$ (uncorrected) (Table 3).

No correlations were found between the mean cortical thickness value of cortical ROIs or subcortical volumes and the clinical characteristics within MDD group.

DISCUSSION

Finding no significant difference in cortical thickness between the first-episode, untreated patients with MDD

Table 1: Demographic and clinical characteristics

	MDD patients (n=20)		Controls (n=20)				
	Mean	SD	Mean	SD	df	t	p
Age	35.4	10.0	38.0	11.2	38	-0.743	0.462
Education (years)	8.8	3.4	9.0	3.0	38	-0.246	0.807
BMI	25.1	5.1	26.0	3.6	38	-0.646	0.522
Sex (Male/Female)	9/11		10/10		1	χ^2=0.100	0.752
Smoker/Nonsmokers	10/10		10/10				
Years of smoking	12.0	5.1	12.7	7.6	18	-0.243	0.811
FTND score	6.3	2.4	4.9	2.3	18	1.349	0.194
Age at onset (years)	34.8	9.5					
Duration of depressive episode (months)	6.1	6.5					
HDRS-17 score	27.3	5.4					

Data are presented as mean±standard deviation unless otherwise indicated.
MDD: Major depressive disorder, BMI: Body mass index, HDRS: Hamilton depression rating scale, FTND: Fagerström test for nicotine dependence, t: Student t test

Table 2: Mean cortical thickness values of cortical ROIs

		MDD patients (n=20)		Controls (n=20)					
		Mean	SD	Mean	SD	f	df	p	Partial Eta squared
Fusiform Gyrus	- Right	2.561	0.146	2.542	0.162	0.038	1.39	0.845	0.001
	- Left	2.641	0.162	2.589	0.118	0.842	1.39	0.364	0.028
Rostral ACC	- Right	2.807	0.194	2.907	0.233	3.029	1.39	0.090	0.073
	- Left	2.942	0.213	2.941	0.219	0.110	1.39	0.741	0.002
Insula	- Right	2.976	0.168	2.898	0.216	1484	1.39	0.231	0.037
	- Left	3.045	0.169	2.956	0.206	1678	1.39	0.203	0.042
Medial OFC	- Right	2.481	0.168	2.463	0.201	0.044	1.39	0.835	0.001
	- Left	2.458	0.191	2.459	0.171	0.057	1.39	0.813	0.001
Rostral MFC	- Right	2.426	0.176	2.374	0.143	0.509	1.39	0.480	0.013
	- Left	2.462	0.159	2.390	0.152	1.473	1.39	0.233	0.037
STC	- Right	2.743	0.185	2.637	0.150	3.205	1.39	0.082	0.077
	- Left	2.736	0.173	2.653	0.170	1.795	1.39	0.189	0.045

Data are presented as mean±standard deviation.
MDD: Major depressive disorder, ACC: Anterior cingulate cortex, OFC: Orbitofrontal cortex, MFC: Middle frontal cortex, STC: Superior temporal cortex, f: A general linear model with age and sex as covariates

Table 3: Subcortical volumes

Hem.	Subcortical Segmentations	MDD group (n=20)		Controls (n=20)		f	df	p	Partial Eta squared
		Mean	SD	Mean	SD				
L	Hippocampus	4.119	379	4.189	411	0.663	1.39	0.421	0.019
	Amygdala	1.410	189	1.388	194	0.068	1.39	0.795	0.002
	Caudate	3.238	333	3.251	414	0.205	1.39	0.653	0.006
	Putamen	4.930	623	4.955	663	0.626	1.39	0.434	0.018
	Pallidum	1.343	235	1.379	202	0.600	1.39	0.444	0.017
	Accumbens	459	84	459	71	0.245	1.39	0.624	0.007
	Thalamus	8.007	853	7.917	828	0.152	1.39	0.669	0.004
R	Hippocampus	4.188	420	4.136	321	0.085	1.39	0.772	0.002
	Amygdala	1.461	173	1.485	177	0.499	1.39	0.484	0.014
	Caudate	3.172	405	3.264	367	1.218	1.39	0.277	0.034
	Putamen	4.848	545	4.776	593	0.005	1.39	0.943	0.001
	Pallidum	1.349	160	1.375	172	1.120	1.39	0.297	0.031
	Accumbens	461	84	484	96	2.336	1.39	0.135	0.063
	Thalamus	6.944	559	6.938	705	0.021	1.39	0.887	0.001

Data are presented as mean±standard deviation, Hem.: Hemisphere
MDD: Major depressive disorder, Hem: Hemisphere, L: Left, R: Right, f: A general linear model with age and sex as covariates

and HC groups is consistent with findings of one previous study (24) but not with others (11,21-23). It is important to note that smoking status and BMI were not controlled in the previous studies. Thus, different results might be partly due to differences in BMI and smoking status between the studies. For example, studies in cigarette smokers examining brain cortical thickness, which is considered to be more sensitive to environmental factors than cortical volume (49), have found reduced thickness of the orbitofrontal cortex (OFC) (50,51), insula, middle temporal gyrus, anterior cingulate cortex, inferior parietal lobule, parahippocampus (51) and bilateral frontal and temporal cortices (52) compared to non-smoker individuals in the community. Similarly, BMI was also found to be negatively associated with cortical thickness in healthy volunteers (53,54). Given that cigarette smoking and obesity are highly prevalent in MDD (33,34), it is possible that some of the differences in cortical thickness between MDD and controls found in previous studies, particularly cortical thinning, may be partly explained by cigarette use and obesity.

There are several other possible explanations for finding no significant difference in cortical thickness between the two groups. One possible reason for the current negative findings could be that the pathological changes may be too subtle to be detected with our sample size or technique during the first depressive episode. Second, cortical thickness might be normal in first-episode patients and change during the course of the disease or with the recurrence of episodes. However, without longitudinal data, we cannot assess the potential non-linear patterns of brain changes that may arise throughout the illness, particularly in the context of a changeable clinical picture. Third, it is important to consider the heterogeneity of MDD. Different types of depressive episodes, such as psychotic, melancholic, atypical, or early and late onset can be associated with reduction or increase in cortical thickness. In conclusion, our results suggest that cortical thickness might be normal at least in some untreated first-episode MDD patients.

To date, only two SBM studies examined the whole-brain cortical surface area in untreated first-episode MDD patients. Similar to our findings, one previous study found no differences between untreated first-episode MDD patients with HC (11) while a recent study found an increased surface area in patients with MDD relative to HC in areas including the right isthmus cingulate region, right superior frontal region, and left inferior parietal region, while a decreased surface area in patients with MDD was observed in areas including the left transverse temporal region and the right inferior parietal region (21). Further studies are required to assess surface area abnormalities at various stages of MDD.

The hippocampus is the most commonly examined subcortical region in previous MDD studies and

hippocampal volume alterations seems to occur most commonly in recurrent or early-onset MDD patients. For example, a recent ENIGMA study with 1728 MDD patients, both first-episode and recurrent, and 7199 healthy controls reported lower mean hippocampal volume in recurrent episode MDD patients but not in first-episode MDD patients. The same study also found hippocampal volume reductions were more pronounced in early-onset patients (<21 years) but not in late-onset patients (>21 years) (27). In line with this, two recent studies with untreated first-episode patients with MDD older than 21 years also did not find any difference in hippocampal volume compared to HC (22,26). Given that the patients in this study were also late-onset patients with MDD, it seems that hippocampal volume reduction is not present in MDD, at least in medication-free, late-onset first-episode patients.

Apart from the hippocampus, in line with our findings a recent ENIGMA study did not detect any significant volume differences between first-episode patients and healthy controls in subcortical gray matter regions including the nucleus accumbens, amygdala, caudate, pallidum, putamen and thalamus (27).The finding of normal amygdala volumes in first-episode, untreated patients with MDD is in contrast with previous studies that found amygdala volume alterations in first-episode patients with MDD (7,55,56). However, recent studies using FreeSurfer did not find any differences in amygdala volume in first-episode patients with MDD compared to HC (22,24,26,27). Unfortunately, subcortical structures other than hippocampus and amygdala are not well studied in first-episode patients with MDD. One recent study found smaller volumes in both thalamus and putamen (26), but studies using FreeSurfer did not replicate these results (22,24,27). Therefore, inconsistencies across studies might be due to different software used for analysis.

The findings of this study should be interpreted after consideration of the following limitations. First, this study was cross-sectional in design, which did not allow us to elucidate the temporal relationships between MDD and brain alterations. Second, the sample size limited the strength of the findings and did not give any opportunity to examine the depression subtypes.

In conclusion, this study provides evidence that cortical thickness, cortical surface area, and subcortical volumes might be normal in first-episode untreated patients with MDD in comparison with well-matched controls, particularly for BMI and smoking status.

Contribution Categories		Author Initials
Category 1	Concept/Design	D.H.D., N.Z., E.B., Z.H.A.
	Data acquisition	D.H.D., P.K.Z., E.P.B., Z.H.A.
	Data analysis/Interpretation	D.H.D., E.B., N.Z.
Category 2	Drafting manuscript	D.H.D., P.K.Z., E.P.B., Z.H.A.
	Critical revision of manuscript	N.Z., E.B.
Category 3	Final approval and accountability	D.H.D., P.K.Z., E.P.B., E.B., Z.H.A., N.Z.
Other	Technical or material support	D.H.D., Z.H.A., P.K.Z., E.P.B.
	Supervision	N/A

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