Cyprus Turkish Journal of Psychiatry & Psychology
Published Online: 03 July 2026, Doi:10.35365/ctjpp.26.3.01

RESEARCH ARTICLE / ARAŞTIRMA MAKALESİ

Evaluation of the Relationship between Depression and the Volume of Olfactory Regions by Parcellation Method

Depresyon ve Koku Bölgeleri Hacmi Arasındaki İlişkinin Parselasyon Yöntemiyle Değerlendirilmesi

Merve Yurt[1], Merve Şahin Can[2], Emrah Özcan[1], Aslıhan Çetinel[1], Esma Gül[3], Ömür Karaca[1], İlter Kuş[1]

Abstract:

Scientific studies in the literature have demonstrated olfactory loss and reduced olfactory bulb volume in individuals with major depressive disorder. This study aims to evaluate the correlation between major depressive disorder and olfactory region volume. In the study, Magnetic Resonance İmaging (MRI) images of 33 patients with major depressive disorder and 33 healthy controls from Balıkesir University Hospital's Mental Health Clinic were retrospectively analyzed. In the obtained MRI series, the volumes of the amygdala, fusiform gyrus, anterior commissure, olfactory radiation, and entorhinal area, which are involved in olfaction, were measured using a parcellation method. All data were transferred to SPSS and analyzed quantitatively. The statistical analysis of the variables examined in the study revealed that the right and left amygdalae tend to be smaller in individuals with illness. It was determined that there was a positive correlation among the parameters evaluated in the study: left amygdala, left entorhinal area, right and left fusiform gyrus volumes, and the Hamilton Depression Scale. As a result of the research, it was revealed in the direction of morphometric analysis that there is a negative relationship between major depressive disorder and olfactory regions. The data obtained in light of these findings will contribute to understanding the cause-and-effect relationship between depression and loss of smell; for clinicians, it is expected to serve as a guide in diagnosis and treatment.

Keywords: Major depression, Olfaction, Magnetic resonance imaging, Parcellation.

[1]Balıkesir University, Faculty of Medicine, Department of Anatomy, Balıkesir, Türkiye.

[2]Balıkesir University, Hospital for Health Practice and Research, Department of Psychiatry, Balıkesir, Türkiye.

[3]Balıkesir University, İvrindi Vocational School of Health Services, Medical Documentation and Secretarial Program, Balıkesir, Türkiye.

Address of Correspondence/Yazışma Adresi: Merve Yurt, Balıkesir University Faculty of Medicine, Morphology Building, Department of Anatomy, Balıkesir University Çağış Campus 10145, Altıeylül/Balıkesir, Türkiye, E-mail: mervetek1607@gmail.com.

Date of Received/Geliş Tarihi: 29.07.2025, **Date of Revision/Düzeltme Tarihi:** 30.11.2025, **Date of Acceptance/Kabul Tarihi:**03.12.2025, **Date of Online Publication/Çevirimiçi Yayın Tarihi:** 03.07.2026

Citing/Referans Gösterimi: Yurt, M., Can, M. Ş., Özcan, E., Çetinel, A., Gül, E., Karaca, Ö., & Kuş, İ. (2026). Evaluation of the relationship between depression and the volume of olfactory regions by parcellation method, *Cyprus Turkish Journal of Psychiatry & Psychology*, 1-8, Doi:10.35365/ctjpp.26.3.01

Öz:

Major depresif bozukluğu bulunan bireylerde koku kaybının görüldüğü ve bulbus olfactorius hacminde küçülme meydana geldiği, literatürde yer alan bilimsel araştırmalarla ortaya konmuştur. Bu çalışmada, majör depresif bozukluk ile koku bölgelerinin hacmi arasındaki korelasyonun değerlendirilmesi amaçlanmaktadır. Çalışmada, Balıkesir Üniversitesi Eğitim ve Araştırma Hastanesi Ruh Sağlığı ve Hastalıkları Polikliniği'nde majör depresif bozukluk tanısı konulan 33 hasta ve kontrol grubunu oluşturacak 33 sağlıklı bireyin Manyetik Rezonans Görüntüleme (MRG) görüntüleri retrospektif olarak incelendi. Elde edilen MRG serilerinde koku duyusunda rol alan amygdala, gyrus fusiformis, commissura anterior, radiatio olfactoria ve entorhinal alan hacmi parselasyon yöntemi kullanılarak ölçüldü. Tüm veriler SPSS yazılımına aktarılarak kantitatif olarak analiz edildi. Araştırmada incelenen değişkenlerin istatistiksel analiz sonuçlarına göre, sağ-sol amigdalaların hasta bireylerde daha küçük hacme sahip olma eğilimi gösterdiği tespit edildi. Çalışmada değerlendirilen parametrelerden, sol amigdala, sol entorhinal alan ve sağ-sol fusiform gyrus hacimleri ile Hamilton Depresyon Ölçeği skalası arasında pozitif bir korelasyon olduğu görüldü. Yapılan araştırmalar neticesinde, majör depresif bozukluk ile koku bölgeleri arasında negatif bir ilişki bulunduğu morfometrik analizler doğrultusunda ortaya konmuştur. Bu veriler ışığında elde edilen verilerin depresyon ve koku kaybı arasındaki neden-sonuç ilişkisinin anlaşılmasına katkıda bulunacağı, klinisyenler açısından ise tanı ve tedavide yol gösterici nitelikte olabileceği düşünülmektedir.

Anahtar Kelimeler: Major depresyon, Koku, Manyetik rezonans görüntüleme, Parselasyon.

Introduction

Major depressive disorder (MDD) is a psychological condition characterized by a combination of emotional and behavioral symptoms. (Ahmed et al., 2017). It is estimated that more than 320 million people worldwide have been diagnosed with MDD, and its prevalence continues to increase over time. (Abdelmotaleb et al., 2020; Dündar et al., 2020). According to the World Health Organization (WHO), MDD is the leading cause of suicide attempts, accounting for approximately 800,000 deaths annually. (Ahmed et al., 2017). Numerous studies have been conducted to elucidate the pathophysiology of MDD. *(*Sağar et al., 2024*)* . Among the hypotheses proposed, the most widely accepted is the monoamine hypothesis, which attributes the disorder to dysregulation in the concentrations of norepinephrine, serotonin, and dopamine. (Boku et al., 2018). However, according to the DSM-5 (Diagnostic and Statistical Manual of Mental Disorders), the diagnosis of MDD requires the presence of at least one of two core symptoms—depressed mood or anhedonia—accompanied by a constellation of additional symptoms. (Lolk, 2013).

Among symptoms not included in the diagnostic criteria for MDD but that adversely affect patients' quality of life are olfactory dysfunction (Athanassi et al., 2021; Kohli et al., 2016; Pause et al., 2001; Schablitzky & Pause, 2014). The prevalence of depression among individuals with olfactory impairment ranges from 40% to 76% (Kohli et al., 2016). These two interconnected phenomena have been the subject of a growing body of literature (Herrmann et al., 2023; Kim & Park, 2021; Negoias et al., 2010; Rochet et al., 2018). The link was first identified in rodents subjected to olfactory bulbectomy, which led to the development of depressive-like behaviors (Kelly et al., 1997). The olfactory system is a chemosensory pathway that converts chemical stimuli into neural signals via central nervous system (CNS) structures (Athanassi et al., 2021). In this pathway, the nervus olfactorius (olfactory nerve) plays a key role in conveying peripheral stimuli to the brain. The term "nervus olfactorius" refers to the delicate nerve fibers, known as fila olfactoria, which are surrounded by meninges and pass through the lamina cribrosa of the ethmoid bone to reach the olfactory bulb (Arıncı & Elhan, 2014). The presence of cholinergic, noradrenergic, and serotonergic innervation within the olfactory bulb suggests a potential link between olfactory dysfunction and the neurotransmitter imbalances described in the monoamine hypothesis of MDD (Li et al., 2020). Changes in serotonin and dopamine levels following bilateral ablation of the olfactory bulb further support this assumption (Rochet et al., 2018).

Cortical areas that are in direct contact with the efferent neurons of the olfactory bulb are collectively defined as the olfactory cortex. These areas include the piriform cortex, amygdala, and entorhinal cortex. Additionally, the hippocampus, a component of the limbic system, is functionally connected to the olfactory cortex. The limbic system, which comprises various interconnected brain structures, regulates emotional and physical responses, including memory, motivation, reward, and sexual behavior. (Arıncı & Elhan, 2014; Erzurumlu et al., 2019; Taner, 2019). Given these associations, the sense of smell is believed to be closely related to emotional states. (Erzurumlu et al., 2019; Schablitzky & Pause, 2014; Soudry et al., 2011; Taalman et al., 2017; Taner, 2019; Yao et al., 2020). A reduction in the number of nerve fibers projecting from the olfactory bulb to the olfactory cortex may lead to atrophy in these regions, potentially resulting in functional impairment of the associated cortical areas. (Rochet et al., 2018; Rottstädt et al., 2018).

In a pivotal 2010 study, it was demonstrated that reduced olfactory bulb volume was associated with diminished olfactory function in MDD patients and correlated with the severity of depressive symptoms. (Negoias et al., 2010) . One proposed mechanism is the olfactory bulb’s inhibitory projections to the amygdala, which are involved in mood regulation. Accordingly, olfactory bulbectomy may lead to disinhibition of the amygdala, resulting in heightened negative emotions such as fear and anxiety. (Pause et al., 2001). The relationship between olfactory dysfunction and MDD is critical to understanding their bidirectional influence. In both cases, dysfunction may lead to a decline in overall quality of life. (Kohli et al., 2016; Sivam et al., 2016).

Despite an increasing number of neuroimaging and clinical studies exploring the relationship between psychiatric disorders and olfactory function, the causal mechanisms remain largely unclear. Based on the current literature, this study hypothesizes that patients diagnosed

with MDD may exhibit reduced volumes in the olfactory cortex. This study aims to morphometrically evaluate structural changes in olfactory cortex regions using magnetic resonance imaging (MRI) in patients with MDD, compare these results with those of healthy individuals, and analyze correlations between volumetric data and depression/anxiety scores. It is anticipated that the findings will contribute valuable insights for clinicians and enrich the existing literature on the etiology of MDD. It is considered that clarifying whether patients with depression exhibit reduced olfactory function, or whether individuals with olfactory dysfunction present depressive symptoms, may help in understanding the underlying mechanisms connecting these conditions.

Materials and Methods

Study Population

This study was conducted using brain MRI scans of individuals diagnosed with major depressive disorder (MDD) and healthy controls, obtained from the Psychiatry Outpatient Clinic at Balıkesir University Training and Research Hospital. The study population included individuals diagnosed with MDD and healthy controls without any personal or first-degree familial history of psychiatric illness. A total of 66 individuals aged between 20 and 74 years, for whom Hamilton Depression Rating Scale (HAM-D) and Hamilton Anxiety Rating Scale (HAM-A) scores were available, were retrospectively evaluated. Before imaging, participants were informed that their images might be used for scientific research and provided written informed consent.

This study was approved by the Non-Interventional Clinical Research Ethics Committee of Balıkesir University (Approval No: EK-2025-272, 01 July 2025) and conducted at the Department of Anatomy, Faculty of Medicine, Balıkesir University.

The HAM-D and HAM-A are among the most widely used instruments for assessing symptom severity. The scores on these scales increase in proportion to the severity of depressive symptoms. (Hamilton, 1960; Shear et al., 2001).

Magnetic Resonance Imaging (MRI) Protocol

MRI scans were acquired using a 1.5 Tesla scanner (Philips, Ingenia, 2013). Anatomical images were obtained using T1-weighted cranial MRI sequences. Coronal T1-weighted images were acquired using a turbo spin echo sequence with the following parameters: repetition time (TR) = 7.0 ms; echo time (TE) = 3.4 ms; field of view (FOV) = 250 × 250 mm; matrix size = 228 × 228; voxel size = 1 × 1 × 1 mm; flip angle = 90°. Slice thickness was set to 1.1 mm with no interslice gap.

Image Evaluation Method

The following olfactory cortex-related regions were bilaterally (right and left) measured using an atlas-based parcellation method: commissura anterior, radiatio olfactoria, amygdala, entorhinal area, gyrus fusiformis, hippocampus, and total brain volume.

Parcellation is a volumetric calculation method based on multiple software tools. One of the primary software packages for this purpose is MRiStudio, which comprises DTIStudio, ROIEditor, and DiffeoMap. DTIStudio is employed to open and save DICOM images obtained from patients. Images are transformed linearly and non-linearly using diffeomorphic metric mapping. Following this transformation, the brain is segmented into 160–180 regions using ROIEditor, and the volume of each region is computed. (Kocaman et al., 2019) . The MRiStudio parcellation protocol has been previously described in earlier studies. (Faria et al., 2011).

Statistical Analysis

The statistical analysis of the data was conducted using SPSS software version 25. Variables with skewness and kurtosis values between −2.0 and +2.0 were considered to have a normal distribution (Suhail & Srinivasulu, 2021) Normally distributed variables were compared between the MDD and healthy groups—regardless of sex—using the Independent Samples t-test. All volumetric data are presented as mean ± standard deviation (SD). The relationship between volumetric variables and scores on the Hamilton Depression and Anxiety Scales was analyzed using Pearson's correlation. A p-value <0.05 was considered statistically significant.

Results

In this study, brain MRI series of a total of 66 individuals aged between 20 and 74 years were evaluated, including 33 patients diagnosed with Major Depressive Disorder (MDD) and 33 healthy controls. The patient group comprised 28 females and 5 males, whereas the control group comprised 17 females and 16 males. The variables analyzed in the study were found to follow normal distributions ($p > 0.05$). The age and scale score distributions of the study population are presented in Table 1.

Table 1. *Age and scale score distribution of the study group*

Study group	n	Age (Mean ± SD)	Hamilton Depression Rating Scale (SD)	Hamilton Anxiety Rating Scale (SD)
Healthy Individuals	33	46.27 ± 14.93	2.30±1.31	3.00±1.14
Patients with Major Depressive Disorder	33	44.30 ± 13.98	17.48±6.03	17.58±6.31

Results of the Independent Samples t-test comparing mean brain region volumes between individuals with MDD and healthy controls—regardless of sex—are provided in Table 2. Table 2 shows that total brain volume, left amygdala volume, and right amygdala volume were reduced in individuals with MDD compared to the control group.

Table 2. *Numerical values comparing the mean volume of olfactory cortex areas between healthy individuals and individuals diagnosed with Major Depressive Disorder*

Brain Region	Healthy Individuals		Individuals Diagnosed with Major Depressive Disorder		p
	n	Avg./SS	n	Avg./SS	
Total Brain Volume	33	1158.92±122.43	33	1093.13±131.01	**0,04***
Left Entorhinal Cortex Volume	33	1.18 ±0.45	33	1.04 ±0.26	0,12
Right Entorhinal Cortex Volume	33	1.56 ±0.41	33	1.45 ±0.36	0,25
Left Gyrus Fusiformis	33	22.01 ±4.36	33	21.07 ±3.68	0,34
Right Gyrus Fusiformis	33	20.73 ±4.55	33	19.56 ±4.58	0,29
Left Amygdala	33	2.50 ±0.47	33	2.20 ±0.44	**0,01***
Right Amygdala	33	2.44 ±0.35	33	2.23 ±0.40	**0,03***
Left Commissura Anterior	33	0.09 ±0.03	33	0.10 ±0.02	0,48
Right Commissura Anterior	33	0.10 ±0.03	33	0.10 ±0.02	0,89
Sol Radiatio Olfactorious	33	0.04 ±0.01	33	0.04 ±0.01	0,20
Right Radiatio Olfactorious	33	0.04 ±0.01	33	0.04 ±0.01	0,21
Left Hippocampus	33	4.32±0.71	33	4.16±0.80	0,38
Right Hippocampus	33	4.48±0.71	33	4.15±0.88	0,10

The correlation analyses between olfactory cortex region volumes and the Hamilton Depression Rating Scale (HAM-D) and Hamilton Anxiety Rating Scale (HAM-A) scores in both the control and MDD groups are presented in Tables 3 and 4, respectively. Statistically significant results are indicated.

Table 3. *Correlation analysis evaluated between the Hamilton Depression and Anxiety Rating Scale and olfactory cortex region volumes of healthy individuals*

		Hamilton Depression Scale	Hamilton Anxiety Scale	Age
Total Brain Volume	r	0,255	0,214	0,091
	p	0,152	0,232	0,613
Left Hippocampus	r	0,226	0,208	-0,007
	p	0,205	0,246	0,970
Right Hippocampus	r	0,271	0,211	0,178
	p	0,127	0,238	0,321
Left Entorhinal area	r	0,177	0,308	-0,249
	p	0,325	0,081	0,162
Right Entorhinal area	r	0,180	0,219	-0,203
	p	0,316	0,220	0,257
Left gyrus fusiformis	r	0,094	0,207	-0,418
	p	0,601	0,247	**0,015***
Right gyrus fusiformis	r	0,086	0,172	-0,482
	p	0,636	0,340	**0,005***
Sol amygdala	r	0,205	0,274	-0,291
	p	0,252	0,122	0,1
Right amygdala	r	0,052	0,187	-0,508
	p	0,772	0,299	**0,003***
Left anterior commissure	r	0,123	0,045	-0,109
	p	0,494	0,802	0,546
Right anterior commissure	r	0,165	0,290	-0,109
	p	0,358	0,101	0,547
Sol radiatio olfactoria	r	-0,47	0,130	-0,241
	p	0,794	0,472	0,178
Right radiatio olfactoria	r	-0,018	0,021	-0,345
	p	0,921	0,909	**0,049***

Table 4. *Correlation analysis of individuals diagnosed with Major Depressive Disorder between the Hamilton Depression and Anxiety Rating Scale and the olfactory cortex region volumes*

		Hamilton Depression Scale	Hamilton Anxiety Scale	Age
Total Brain Volume	r	0,139	0,09	0,059
	p	0,441	0,618	0,744
Left Hippocampus	r	0,238	0,140	-0,005
	p	0,183	0,436	0,978
Right Hippocampus	r	0,04	0,039	0,118
	p	0,825	0,829	0,515
Left Entorhinal area	r	0,377	0,293	-0,038
	p	**0,031***	0,097	0,834
Right Entorhinal area	r	0,145	0,021	-0,124
	p	0,420	0,907	0,492
Left gyrus fusiformis	r	0,432	0,317	-0,104
	p	**0,012***	0,072	0,563
Right gyrus fusiformis	r	0,367	0,173	-0,125
	p	**0,036***	0,337	0,49
Sol amygdala	r	0,401	0,327	0
	p	**0,021***	0,063	0,999
Right amygdala	r	0,334	0,276	0,044
	p	0,057	0,120	0,806
Left anterior commissure	r	0,318	0,224	0,004
	p	0,071	0,210	0,981
Right anterior commissure	r	0,073	0,124	-0,214
	p	0,687	0,491	0,232
Sol radiatio olfactoria	r	0,246	-0,068	-0,182
	p	0,168	0,705	0,312
Right radiatio olfactoria	r	-0,054	-0,227	0,166
	p	0,763	0,204	0,356

As a result of the study, a positive correlation was identified within the MDD group between HAM-D scores and the volumes of the left entorhinal area, left fusiform gyrus, right fusiform gyrus, and left amygdala—all subregions of the olfactory cortex. In individuals with MDD, the volume of these regions increased with increasing HAM-D scores. In the control group, correlation analysis with age revealed negative correlations between age and the volumes of the right and left fusiform gyri, the right amygdala, and the right radiatio olfactoria. These findings suggest that the volumes of these brain regions decrease with advancing age.

Discussion

In the present study, brain MRI images of individuals diagnosed with Major Depressive Disorder (MDD) and healthy controls were analyzed using a parcellation method to evaluate the volumes of brain regions involved in olfactory processing. These volumes were then compared with scores from the Hamilton Depression Rating Scale (HAM-D) and Hamilton Anxiety Rating Scale (HAM-A). As a result of the study, the right and left amygdalae and total brain volume were more atrophic in individuals with MDD. Correlation analyses revealed positive associations between HAM-D scores and volumes of the left entorhinal cortex, bilateral fusiform gyri, and left amygdala in the MDD group.

The amygdala is one of the most frequently associated brain regions with depression, and its morphometric evaluation is therefore of considerable importance. However, inconsistencies exist in the literature regarding the amygdala (Gray et al., 2020; Höflich et al., 2012; Schablitzky & Pause, 2014). Some studies have reported increases in volume in the early stages of MDD and decreases in the later stages (Monkul et al., 2007; Weniger et al., 2006). While specific studies have reported increases in amygdalar volume following pharmacological treatment, others have found no significant volumetric differences between patient and control groups (Hamilton et al., 2008). Functional MRI (fMRI) studies have indicated that amygdala activity tends to decrease with age (Barresi et al., 2012). In the present study, volumes of the right and left amygdala were reduced in individuals with MDD compared with healthy controls. However, a positive correlation between HAM-D scores and left amygdala volume was observed within the patient group. Although amygdala volumes were lower in the patient group than in controls, the finding that left amygdala volume increases with depression severity within the MDD group may reflect compensatory mechanisms, such as hyperactivity or functional compensation (Van Eijndhoven et al., 2009). Additional factors such as disease stage, age, sex, and antidepressant use may also influence regional brain volumes (Hamilton et al., 2008; Vythilingam et al., 2004). Furthermore, the amygdala has been shown to exhibit age- and sex-related variability, which may influence volumetric outcomes (Fujita et al., 2023; Ritchie et al., 2018).

The fusiform gyrus, traditionally associated with facial recognition, has more recently been implicated in olfactory processing. Previous studies have reported reduced gray matter volume in the fusiform gyrus in patients with depression. (Moorhead et al., 2007) Other studies have shown that fusiform gyrus volume is reduced in patients with olfactory dysfunction, that it is activated during olfactory stimulation in fMRI studies, and that cortical thickness can increase following olfactory training. (Al Aïn et al., 2019). In the present study, a positive correlation was found between HAM-D scores and fusiform gyrus volume, suggesting that as MDD severity increases,

fusiform gyrus volume also increases. A 2021 study reported a negative correlation between fusiform gyrus volume and negative symptom severity in patients with schizophrenia. (Jung et al., 2021). However, no studies have yet reported a direct correlation between fusiform gyrus volume and HAM-D scores in patients with MDD.

The entorhinal cortex and hippocampus, which form part of the entorhinal-hippocampal circuit, play critical roles in memory and mood regulation. (Kim & Park, 2021). Although reductions in hippocampal and entorhinal cortex volumes were observed in the MDD group compared to controls, these differences were not statistically significant. However, a positive correlation was found between left entorhinal cortex volume and HAM-D scores within the MDD group. This could be influenced by factors such as sample size, antidepressant use, and age- and sex-related individual variability. (Barresi et al., 2012; Lorenzetti et al., 2009; Vythilingam et al., 2004). There is evidence in the literature indicating that the use of antidepressants in depression may lead to an increase in hippocampal volume; however, no studies have been found demonstrating a direct effect of antidepressants on the volume of the entorhinal cortex. A review of the literature reveals that patients diagnosed with major depressive disorder (MDD) often exhibit a reduction in hippocampal volume. (Croy et al., 2013; Gray et al., 2020; Lorenzetti et al., 2009), and that there is an association between the volume of this region and depressive symptoms (Besteher et al., 2019) , which is consistent with the hippocampal volume reduction observed in our study. Nevertheless, studies also report no significant differences in hippocampal volume between patients and healthy controls. (Brown et al., 2019; Tannous et al., 2020).

The radiatio olfactoria, which comprises fibers extending from the olfactory bulb to the olfactory cortex, showed no statistically significant volumetric differences between MDD patients and healthy controls. Furthermore, the volumetric assessment of the olfactory bulb in patients with MDD remains largely unexplored in the literature.

MDD is a diagnostically challenging disorder, as diagnosis relies heavily on patients' self-reported symptoms and the clinician's expertise. For this reason, investigations into morphological differences in the brain are crucial for differentiating MDD patients from healthy individuals. High-resolution MRI, functional MRI, and Diffusion Tensor Imaging (DTI) are valuable tools for early identification of brain abnormalities and for detailed evaluation of disease progression. (Van der Kolk et al., 2013) However, their widespread clinical use is often limited by high cost and technical challenges. (Cattarinussi et al., 2021). In this study, a more accessible 1.5-T MRI scanner was used. Historically, MRI was employed to exclude surgically treatable causes of cognitive impairment. Today, MRI also supports the diagnosis of neuropsychiatric disorders by revealing structural cerebral changes, and its advantages include radiation-free, non-invasive, and repeatable imaging. (Johnson et al., 2012).

Conclusion

This study found that the right and left amygdala volumes, as well as total brain volume, were significantly smaller in individuals with MDD than in healthy controls. Correlation analysis within the patient group revealed positive associations between HAM-D scores and volumes of the left entorhinal cortex, bilateral fusiform gyri, and left amygdala. In other words, as depression severity increased, the volumes of these brain regions also increased. Although these regions were found to be smaller in volume in the patient group compared to controls, the observed positive correlation should not be interpreted as contradictory, as the analysis was conducted within the MDD group, not between groups. The study also emphasizes that multiple factors influence volumetric changes in these brain regions.

Based on this study's findings, atrophy in olfactory-related brain regions may occur in individuals with MDD, and these changes may serve as potential biomarkers for the disorder. In this study, the relationship between the morphometric characteristics of the examined parameters and depression scale scores was evaluated, and the results were demonstrated through statistical analysis. In this context, the findings are considered to clarify the relationship between depression severity and olfactory function. Clinical prospective studies with larger sample sizes and more comprehensive assessments of disease severity and olfactory function will provide more substantial contributions to elucidating the etiology. To further clarify the link between MDD and olfaction, future studies combining clinical assessments with advanced neuroimaging methods are warranted.

Limitations

Because this study was retrospective, data on antidepressant use, disease stage, and olfactory dysfunction among MDD patients were not available. Sociodemographic data other than age and sex could not be obtained for the participants. Furthermore, the relatively small sample size may have influenced the findings. Additionally, because the automated brain segmentation method did not include the olfactory bulb, we were unable to measure its volume. The study results should therefore be interpreted with these limitations in mind.

Declarations

Conflict of Interest Statement
The authors declare no conflicts of interest regarding the publication of this study.

Funding
This study received no external funding.

Ethical Approval
Ethical approval for this study was obtained from the Non-Interventional Research Ethics Committee of the Health Sciences Directorate, Balıkesir University, on July 1, 2025 (Approval No: 2025/272).

Consent to Participation
This study was conducted retrospectively. Informed consent forms for Magnetic Resonance Imaging (MRI) examinations were obtained from all participants. Permission was granted to use the imaging data for scientific research. Additionally, institutional approval was obtained to access and utilize the images.

Consent to Publication
Not applicable.

Availability of Data and Materials
The data are available from the corresponding author upon

reasonable request, subject to the institution's permission.

Authors' Contributions

MY, MSC, and EO conceived and designed the study. MY, AÇ, and EG contributed substantially to the literature review and the drafting of the manuscript. MY, MSC, and EO were responsible for data collection and conducted the statistical analyses. MY, ÖK, and İK provided critical revisions to the manuscript. All authors have read, reviewed, and approved the final version of the manuscript.

References

Abdelmotaleb, M. A. M., Fadeel, N. A., Abdel Naem, M. M., & Said, H. M. (2020). Sociodemographic and clinical characteristics of a sample of patients with major depressive disorder. *Minia Journal of Medical Research*, 31(2), 8–11. https://doi.org/10.21608/mjmr.2022.220825

Ahmed, H. U., Hossain, M. D., Aftab, A., Soron, T. R., Alam, M. T., Chowdhury, M. W., & Uddin, A. (2017). Suicide and depression in the World Health Organization South-East Asia region: A systematic review. *WHO South-East Asia Journal of Public Health*, 6(1), 60–66. https://doi.org/10.4103/2224-3151.206167

Al Aïn, S., Poupon, D., Hétu, S., Mercier, N., Steffener, J., & Frasnelli, J. (2019). Smell training improves olfactory function and alters brain structure. *Neuroimage*, 189, 45–54. https://doi.org/10.1016/j.neuroimage.2019.01.008

Arıncı, K., & Elhan, A. (2014). Anatomi: duyu organları. Güneş Kitabevi, Ankara, Türkiye. ISBN: 978-975-277-514-5

Athanassi, A., Dorado Doncel, R., Bath, K. G., & Mandairon, N. (2021). Relationship between depression and olfactory sensory function: a review. *Chem Senses*, 46. https://doi.org/10.1093/chemse/bjab044

Barresi, M., Ciurleo, R., Giacoppo, S., Foti Cuzzola, V., Celi, D., Bramanti, P., & Marino, S. (2012). Evaluation of olfactory dysfunction in neurodegenerative diseases. J Neurol Sci, 323(1-2), 16–24. https://doi.org/10.1016/j.jns.2012.08.028

Besteher, B., Squarcina, L., Spalthoff, R., Bellani, M., Gaser, C., Brambilla, P., & Nenadić, I. (2019). Hippocampal volume as a putative marker of resilience or compensation to minor depressive symptoms in a nonclinical sample. *Frontiers in Psychiatry*, 10, 467. https://doi.org/10.3389/fpsyt.2019.00467

Boku, S., Nakagawa, S., Toda, H., & Hishimoto, A. (2018). Neural basis of major depressive disorder: Beyond monoamine hypothesis. *Psychiatry and clinical neurosciences*, 72(1), 3–12. https://doi.org/10.1111/pcn.12604

Brown, S. S., Rutland, J. W., Verma, G., Feldman, R., Alper, J., Schneider, M., Delman, B. N., Murrough, J., & Balchandani, P. (2019). Structural MRI at 7T reveals amygdala nuclei and hippocampal subfield volumetric association with major depressive disorder symptom severity. *Scientific reports*, 9(1), 10166. https://doi.org/10.1038/s41598-019-46687-7

Cattarinussi, G., Delvecchio, G., Maggioni, E., Bressi, C., & Brambilla, P. (2021). Ultra-high field imaging in major depressive disorder: a review of structural and functional studies. *Journal of Affective Disorders*, 290, 65–73. https://doi.org/10.1016/j.jad.2021.04.056

Croy, I., Yarina, S., & Hummel, T. (2013). Enhanced parosmia and phantosmia in patients with severe depression. *Psychol Med*, 43(11), 2460–2464. https://doi.org/10.1017/s0033291713001773

Dündar, M. A., İlhan, M. N., & Karamüftüoğlu, N. (2020). The Prevalence And Possıble Rısk Factors Of Depressıon And Anxıety Dısorders In Syrıan Mıgrant Women In Turkey. *Kıbrıs Türk Psikiyatri ve Psikoloji Dergisi*, 2(1), 14–19. https://doi.org/https://doi.org/10.35365/ctjpp.20.2.2

Erzurumlu, R., Şengül, G., & Ulupınar, E. (2019). *Nöroanatomi*. Ankara, Türkiye. ISBN:978-975-277-747-7

Faria, A. V., Hoon, A., Stashinko, E., Li, X., Jiang, H., Mashayekh, A., Akhter, K., Hsu, J., Oishi, K., & Zhang, J. (2011). Quantitative analysis of brain pathology based on MRI and brain atlases—applications for cerebral palsy. *Neuroimage*, 54(3), 1854-1861. https://doi.org/10.1016/j.neuroimage.2010.09.061

Fujita, S., Mori, S., Onda, K., Hanaoka, S., Nomura, Y., Nakao, T., Yoshikawa, T., Takao, H., Hayashi, N., & Abe, O. (2023). Characterization of brain volume changes in aging individuals with normal cognition using serial magnetic resonance imaging. *JAMA Network Open*, 6(6), e2318153-e2318153. doi: https://doi.org/10.1001/jamanetworkopen.2023.18153

Gray, J. P., Müller, V. I., Eickhoff, S. B., & Fox, P. T. (2020). Multimodal Abnormalities of Brain Structure and Function in Major Depressive Disorder: A Meta-Analysis of Neuroimaging Studies. *The American Journal of Psychiatry*, 177(5), 422–434. https://doi.org/10.1176/appi.ajp.2019.19050560

Hamilton, J. P., Siemer, M., & Gotlib, I. H. (2008). Amygdala volume in major depressive disorder: a meta-analysis of magnetic resonance imaging studies. *Molecular Psychiatry*, 13(11), 993–1000. http://dx.doi.org/10.1038/mp.2008.57

Hamilton, M. (1960). A rating scale for depression. J*ournal of Neurology, Neurosurgery, and Psychiatry*, 23(1), 56. https://doi.org/10.1136/jnnp.23.1.56

Herrmann, T., Koeppel, C., Linn, J., Croy, I., & Hummel, T. (2023). Olfactory brain activations in patients with major depressive disorder. *Scientific reports*, 13(1), 10072. https://doi.org/10.1038/s41598-023-36783-0

Höflich, A., Baldinger, P., Savli, M., Lanzenberger, R., & Kasper, S. (2012). Imaging treatment effects in depression. *Reviews in the Neurosciences*, 23(3), 227–252. https://doi.org/10.1515/revneuro-2012-0038

Johnson, K. A., Fox, N. C., Sperling, R. A., & Klunk, W. E. (2012). Brain imaging in Alzheimer's disease. *Cold Spring Harbor Perspectives in Medicine*, 2(4), a006213. https://doi.org/10.1101/cshperspect.a006213

Jung, S., Kim, J.-H., Kang, N.-O., Sung, G., Ko, Y.-G., Bang, M., Park, C. I., & Lee, S.-H. (2021). Fusiform gyrus volume reduction associated with impaired facial expressed emotion recognition and emotional intensity recognition in patients with schizophrenia spectrum psychosis. *Psychiatry Research: Neuroimaging*, 307, 111226. https://doi.org/10.1016/j.pscychresns.2020.111226

Kelly, J. P., Wrynn, A. S., & Leonard, B. E. (1997). The olfactory bulbectomized rat as a model of depression: an update. *Pharmacol Ther*, 74(3), 299–316. https://doi.org/10.1016/s0163-7258(97)00004-1

Kim, I. B., & Park, S.-C. (2021). The entorhinal cortex and adult neurogenesis in major depression. International *Journal of Molecular Sciences*, 22(21), 11725. https://doi.org/10.3390/ijms222111725

Kocaman, H., Acer, N., Köseoğlu, E., Gültekin, M., & Dönmez, H. (2019). Evaluation of intracerebral ventricles volume of patients with Parkinson's disease using the atlas-based method: A methodological study. *Journal of Chemical Neuroanatomy*, 98, 124–130. https://doi.org/10.1016/j.jchemneu.2019.04.005

Kohli, P., Soler, Z. M., Nguyen, S. A., Muus, J. S., & Schlosser, R. J. (2016). The association between olfaction and depression: a systematic review. *Chemical Senses*, 41(6), 479–486. https://doi.org/10.1093/chemse/bjw061

Li, A., Rao, X., Zhou, Y., & Restrepo, D. (2020). Complex neural representation of odor information in the olfactory bulb. Acta Physiol (Oxf), 228(1), e13333. https://doi.org/10.1111/apha.13333

Lolk, A. (2013). Neurokognitive lidelser. In the Diagnostic and statistical manual of mental disorders. *American Psychiatric Association*. https://doi.org/10.1176/appi.books.9780890425596

Lorenzetti, V., Allen, N. B., Fornito, A., & Yücel, M. (2009). Structural brain abnormalities in major depressive disorder: a selective review of recent MRI studies. *Journal of Affective Disorders*, 117(1-2), 1–17. https://doi.org/10.1016/j.jad.2008.11.021

Monkul, E., Hatch, J. P., Nicoletti, M. A., Spence, S., Brambilla, P., Lacerda, A. d., Sassi, R. B., Mallinger, A., Keshavan, M., & Soares, J. C. (2007). Fronto-limbic brain structures in suicidal and non-suicidal female patients with major depressive disorder. *Molecular Psychiatry*, 12(4), 360–366. https://doi.org/10.1038/sj.mp.4001919

Moorhead, T. W. J., McKirdy, J., Sussmann, J. E., Hall, J., Lawrie, S. M., Johnstone, E. C., & McIntosh, A. M. (2007). Progressive gray matter loss in patients with bipolar disorder. *Biological Psychiatry*, 62(8), 894–900. https://doi.org/10.1016/j.biopsych.2007.03.005

Negoias, S., Croy, I., Gerber, J., Puschmann, S., Petrowski, K., Joraschky, P., & Hummel, T. (2010). Reduced olfactory bulb volume and olfactory sensitivity in patients with acute major depression. *Neuroscience*, 169(1), 415–421. https://doi.org/10.1016/j.neuroscience.2010.05.012

Pause, B. M., Miranda, A., Göder, R., Aldenhoff, J. B., & Ferstl, R. (2001). Reduced olfactory performance in patients with major depression. *Journal of Psychiatric Research*, 35(5), 271-277. https://doi.org/10.1016/S0022-3956(01)00029-2

Ritchie, S. J., Cox, S. R., Shen, X., Lombardo, M. V., Reus, L. M., Alloza, C., Harris, M. A., Alderson, H. L., Hunter, S., & Neilson, E. (2018). Sex differences in the adult human brain: evidence from 5216 UK Biobank participants. *Cerebral Cortex*, 28(8), 2959–2975. https://doi.org/10.1093/cercor/bhy109

Rochet, M., El-Hage, W., Richa, S., Kazour, F., & Atanasova, B. (2018). Depression, olfaction, and quality of life: a mutual relationship. *Brain Sciences*, 8(5), 80. https://doi.org/10.3390/brainsci8050080

Rottstädt, F., Han, P., Weidner, K., Schellong, J., Wolff-Stephan, S., Strauß, T., Kitzler, H., Hummel, T., & Croy, I. (2018). Reduced olfactory bulb volume in depression: A structural moderator analysis. *Hum Brain Mapp*, 39(6), 2573–2582. https://doi.org/10.1002/hbm.24024

Sağar, M. E., Kaya, F., Eroğlu, Y., Sinan, D., Çelik, Y., & Tosun, C. (2024). Examining the predictive role of depression on smartphone addiction. *Kıbrıs Türk Psikiyatri ve Psikoloji Dergisi*, 6(2), 156–165. https://doi.org/https://doi.org/10.35365/ctjpp.24.2.06

Schablitzky, S., & Pause, B. M. (2014). Sadness might isolate you in a non-smelling world: olfactory perception and depression. *Frontiers in Psychology*, 5, 45–45. https://doi.org/10.3389/fpsyg.2014.00045

Shear, M. K., Vander Bilt, J., Rucci, P., Endicott, J., Lydiard, B., Otto, M. W., Pollack, M. H., Chandler, L., Williams, J., & Ali, A. (2001). Reliability and validity of a structured interview guide for the Hamilton Anxiety Rating Scale (SIGH-A). *Depression and Anxiety*, 13(4), 166–178. https://doi.org/10.1002/da.1033

Sivam, A., Wroblewski, K. E., Alkorta-Aranburu, G., Barnes, L. L., Wilson, R. S., Bennett, D. A., & Pinto, J. M. (2016). Olfactory dysfunction in older adults is associated with feelings of depression and loneliness. *Chemical Senses*, 41(4), 293–299. https://doi.org/10.1093/chemse/bjv088

Soudry, Y., Lemogne, C., Malinvaud, D., Consoli, S.-M., & Bonfils, P. (2011). Olfactory system and emotion: common substrates. *European Annals of Otorhinolaryngology, Head and Neck Diseases*, 128(1), 18–23. https://doi.org/10.1016/j.anorl.2010.09.007

Suhail, P., & Srinivasulu, Y. (2021). Perception of service quality, satisfaction, and behavioral intentions in Ayurveda healthcare. *Journal of Ayurveda and Integrative Medicine*, 12(1), 93–101. https://doi.org/10.1016/j.jaim.2020.10.011

Taalman, H., Wallace, C., & Milev, R. (2017). Olfactory Functioning and Depression: A Systematic Review [Review]. 8. https://doi.org/10.3389/fpsyt.2017.00190

Taner, D. (2019). Fonksiyonel Nöroanatomi (23. ed.). ODTÜ Yayıncılık, Ankara, Türkiye. ISBN 978-975-7064-05-3

Tannous, J., Godlewska, B. R., Tirumalaraju, V., Soares, J. C., Cowen, P. J., & Selvaraj, S. (2020). Stress, inflammation, and hippocampal subfields in depression: A 7 Tesla MRI Study. *Translational Psychiatry*, 10(1), 78. https://doi.org/10.1038/s41398-020-0759-0

Van der Kolk, A. G., Hendrikse, J., Zwanenburg, J. J., Visser, F., & Luijten, P. R. (2013). Clinical applications of 7 T MRI in the brain. *European Journal of Radiology*, 82(5), 708–718. https://doi.org/10.1016/j.ejrad.2011.07.007

Van Eijndhoven, P., van Wingen, G., van Oijen, K., Rijpkema, M., Goraj, B., Verkes, R. J., Oude Voshaar, R., Fernández, G., Buitelaar, J., & Tendolkar, I. (2009). Amygdala volume marks the acute state in the early course of depression. *Biological Psychiatry*, 65(9), 812–818. https://doi.org/10.1016/j.biopsych.2008.10.027

Vythilingam, M., Vermetten, E., Anderson, G. M., Luckenbaugh, D., Anderson, E. R., Snow, J., Staib, L. H., Charney, D. S., & Bremner, J. D. (2004). Hippocampal volume, memory, and cortisol status in major depressive disorder: effects of treatment. *Biological Psychiatry*, 56(2), 101–112. https://doi.org/10.1016/j.biopsych.2004.04.002

Weniger, G., Lange, C., & Irle, E. (2006). Abnormal size of the amygdala predicts impaired emotional memory in major depressive disorder. *Journal of Affective Disorders*, 94(1-3), 219–229. https://doi.org/10.1016/j.jad.2006.04.017

Yao, Z., Fu, Y., Wu, J., Zhang, W., Yu, Y., Zhang, Z., Wu, X., Wang, Y., & Hu, B. (2020). Morphological changes in subregions of the hippocampus and amygdala in major depressive disorder patients. *Brain Imaging and Behavior*, 14(3), 653–667. https://doi.org/10.1007/s11682-018-0003-1