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Research article

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Cerebellum and nucleus caudatus asymmetry in major depressive disorder

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The study was approved by the RTEU Faculty of Medicine Ethics Committee Decision No. 2020/13.
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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Abstract

Background/Aim: The relationship between major depressive disorder (MDD) and specific brain regions was investigated using neuroimaging methods. Although the findings show structural hemispheric asymmetry, research has often focused on the specific brain region involved in MDD. This study aimed to investigate asymmetry in the brain regions of MDD patients for the first time with volBrain, which is a fully automated segmentation technique.

Methods: Our study was designed as a case-control study. Structural asymmetry was evaluated using the current web-based fully automated segmentation algorithm, volBrain, that analyzes volumetric T1 axial magnetic resonance imaging data. Sixteen cases with MDD and 14 healthy controls were analyzed. For comparison of continuous data between binary groups, an independent T-test was used for data that follow a normal distribution and Mann–Whitney U (MWU) test was used for data that did not follow a normal distribution while categorical data were evaluated using Chi-square test (or Fisher's exact test when needed).

Results: There was no significant difference in terms of gender ($\chi 2$ [1, n = 30] = 0.117, P = 0.732), education level (2 [1, n = 30] = 0.002; P = 0.961] and marital status (P = 0.596, Fisher exact chi-square test). However, both groups were found to be similar in terms of age (P = 0.608, MWU test). Right/left nucleus caudatus volume ratios (P = 0.028, MWU test) and right/left cerebellum volume ratios were significantly smaller in the case group (P = 0.006, independent T-test). When the volumes of the right and left parts were compared, only the volume of the right globus pallidus was larger (statistically significant) in the case group (P = 0.008, independent T-test).

Conclusion: In line with our hypothesis, our study supports the notion of cortico–striatal–pallidal–thalamic circuit abnormalities in current MDD research and found that some regions in this phase may contain structural asymmetry. In addition, this study contributed to the literature consisting of studies that have examined the relationship between cerebellum and MDD by adding that the cerebellum may show structural asymmetry. The results of our study suggest that research using volBrain may be beneficial to patients with MDD. Current web-based fully automatic segmentation algorithms can restrict both the rater-induced differences in manual segmentation applications and the differences that various segmentation algorithms can create. The challenge of multicenter research can be overcome by using web-based fully automated segmentation volumetry systems and data containing the same standardized magnetic resonance imaging (MRI) acquisition parameters because it is easy for clinicians around the world to access web-based fully automated segmentation volumetry systems. Research on fully automatic segmentation techniques might be the driving force behind fully understanding biological foundations of MDD in the future.

Keywords: Asymmetrical, Cerebellum, Depression, Nucleus caudatus, volBrain

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Introduction

Major depressive disorder (MDD) is one of the psychiatric disorders with a chronic course that is common throughout an MDD patient's life and is accompanied by severe impairment in functionality [1]. Although many comprehensive studies have been conducted, the etiology of MDD remains uncertain, and research concerning this subject is ongoing [2]. Although the factors that play a role in the development of the disorder cannot be revealed exactly, MDD is thought to be a multifactorial disorder that can be induced by the interaction of biological, psychological, and social factors [3]. Many neuroimaging techniques have been used, including structural magnetic resonance imaging (sMRI), functional MRI (fMRI), magnetic resonance spectroscopy (MRS), diffusion tensor imaging (DTI), positron emission tomography (PET), and near infrared spectroscopy (NIRS) in studies examining the biological basis of MDD [4]. Noninvasive neuroimaging studies have shown that various behavioral patterns seen in MDD patients may be associated with structural and functional abnormalities in specific brain regions [5–7].

Although asymmetry is a common aspect of the human brain, asymmetry abnormalities are a condition that is particularly emphasized in MDD patients and can be demonstrated by MRI studies in some psychiatric disorders [8]. Studies conducted using neuroimaging techniques and designed on the basis of a hypothesis based on the relationship between emotions and brain lateralization have shown that structural and functional asymmetries between hemispheres can be found in MDD patients [9–12]. Numerous studies using neurocognitive, electrophysiological, and neuroimaging measurements in MDD patients provide evidence of functional brain asymmetry abnormalities [13]. Although the hypothesis that many cognitive and emotional functions are performed asymmetrically between the left and right hemispheres has a long history, this hypothesis should still be evaluated [9]. Some researchers think that brain asymmetry reveals different clinical manifestations of different psychiatric disorders as a result of similar differences in brain function [14, 15]. In this context, right hemisphere hyperactivity/left hemisphere hypoactivity stands out as a feature frequently detected in MDD neuroimaging studies [14]. Although hemispheric asymmetry abnormalities have been shown in MDD neuroimaging studies, most neuroimaging studies were established to evaluate detailed structural asymmetry in the whole brain [2, 8, 16]. Anatomical studies in MDD patients report that volumetric changes in gray matter are frequently observed in cortical-limbic areas such as the anterior cingulate cortex, dorsolateral prefrontal cortex, orbitofrontal cortex, amygdala, thalamus and putamen [17–20]. A recent sMRI study showed that abnormalities in structural asymmetry seen in MDD patients involve the cortico–striatal–pallidal–thalamic circuit [14]. Structural hemispheric asymmetry can be a biological marker of MDD as studies showing that this asymmetry is present in patients with MDD in remission, and in babies of mothers with MDD have been published [9]. Recent research has increasingly emphasized the relationship between the cerebellum and MDD; nevertheless, studies examining cerebellar dimensions in MDD are very few [21, 22]. While early MRI studies showed that \cerebellar size decreased in patients with MDD, a recent quantitative MRI study did not reveal a statistically significant difference between MDD and control patients [23]. A voxel-based morphometry study that followed the earlier studies indicated that the left cerebellum gray matter volume may decrease in MDD and the left cerebellar hemisphere may play a role in MDD pathophysiology [24].

Although the gold standard for volumetric measurement of brain structures is considered to be manual segmentation techniques, such procedures have a number of limitations due to different concerns, such as differences between the relevant evaluators and the significant need for anatomical and methodological expertise of the assessor [25, 26]. Manual segmentation requires a significant time requirement that can limit the review and standardization of large data sets [25]. To overcome these limitations, several automatic techniques, which can be segmented into regional computer structures, can be used [27, 28]. Several automatic segmentation algorithms, such as volBrain, FIRST, FSL-ANAT, Freesurfer and MRIcloud, were developed to identify MRI brain data analysis in an objective, reliable, and repeatable manner [25, 29, 30]. Studies have been published showing that the closest and highest accuracy rate of manual segmentation measurements can be achieved by volBrain analysis among fully automated segmentation applications [29, 31]. VolBrain is a web-based MRI brain volumetric system that provides rapid volumetric measurements with reference values based on a contrast free three-dimensional T1 gradient echo image [32].

The purpose of this study was to investigate past findings addressing the relationship between MDD and emotions with emphasis on brain lateralization and especially, regional brain asymmetry, which is emphasized to be observed in cortico–striatal–pallidal–thalamic circuits with the newly developed fully automated segmentation technique, volBrain. In addition, due to the lack of adequate research in this field with the increased emphasis on the recent relationship between the cerebellum and MDD, it was also aimed to evaluate possible cerebellar asymmetry using volBrain in MDD patients in our study. As we know, our research is the first study investigating brain volumes using the volBrain method in MDD. For this reason, it is thought that our study will enable the comparison of volBrain findings related to MDD with the results of sMRI study and contribute to the potential use of volBrain in scientific research.

Materials and methods

Participants

Within the scope of our study, the cases recorded between September 25, 2016, and January 22, 2020, in the Psychiatric Outpatient Clinic and Picture Archiving Communication Systems (PACS) of Recep Tayyip Erdogan University (RTEU) Education and Research Hospital were retrospectively examined. In our study, data from recorded cases were examined in our hospital automation system between the specified dates. Those cases diagnosed with MDD (ICD-10: F32.0 in the hospital automation system) based on the structured clinical interview questionnaire (SCID-I) according to DSM-IV criteria were included in the study. Criteria for study inclusion for MDD patients included patients between the ages of 18 and

85, literate, without additional psychiatric, neurological, and/or significant physical disease (cancer, diabetes mellitus, liver failure, renal failure, hypertension, endocrine disease, and others), no history of suicide attempts, not pregnant or lactating, not undergoing medical treatment, and no substance use/abuse. PACS included 16 cases with volumetric axial T1 sequence brain imaging data taken with the 3 Tesla GE Discovery Magnetic Resonance (MR) 750W GEM ENAB device. Brain MRIs are normally reported by specialist radiologists working in the Radiology Department. Similarly, healthy (control) subjects included 14 people who were between the ages of 18 and 85 and literate, without additional psychiatric, neurological, or significant physical disease (cancer, diabetes mellitus, liver failure, renal failure, hypertension, endocrine disease, and others), no history of suicide attempts, not pregnant or lactating, not undergoing medical treatment, and no substance use/abuse. PACS included healthy subjects with volumetric axial T1 sequence brain imaging data obtained with the 3 Tesla GE Discovery Magnetic Resonance (MR) 750W GEM ENAB device. Brain MRIs are normally reported by specialist radiologists working in the Radiology Department. A total of 30 (patients and controls) volumetric axial T1 sequence brain imaging data taken with 3 Tesla GE Discovery Magnetic Resonance (MR) 750W GEM ENAB devices were compared using the volBrain analysis algorithm. The study was carried out in compliance with the Declaration of Helsinki. The study was approved by the RTEU Faculty of Medicine Ethics Committee Decision No. 2020/13. All patients in the study were informed about the study, and their written informed consent was obtained. The authors declare that they have no known competing financial interests or personal relationships that could have influenced the work reported in this paper.

Measures and Procedures

Psychiatric Evaluation and Data Registration Form: This form was prepared by our group and aimed to evaluate the compliance of the sociodemographic data of the cases according to the inclusion and exclusion criteria. Sixteen patients who had records in the automation system of the hospital and met the inclusion criteria (ICD-10: F32.0 in the hospital automation system) were included in the study.

Implementation: The patients who had psychiatric outpatient application records in the automation system of RTEU Faculty of Medicine Training and Research Hospital and who were diagnosed with MDD based on SCID-I during their application and who were thought to meet the study criteria were identified [33]. Patients who had phone numbers accessed in the hospital file information system received a phone call. Patients who chose to participate in the study during the phone call were invited to the psychiatry outpatient clinic to evaluate the study criteria in detail. Patients found to fulfill the study criteria were included in the study.

Neuroimaging - MRI acquisition parameters: Cranial MRI examination was performed using 36-channel head coil with 3 Tesla Discovery MR 750W, GEM-70, (General Electric Company, USA). The volumetric T1 axial (AX 3D T1 BRAVO) image obtaining parameters used for research included several parameters: (1) FOV: 24, Fhase FOV: 1.00, (2) Slice Thickness: 1 mm, (3) EN: 9.0, TE: 3.6, (4) Flip Angle: 12, (5) Frequency:288, (6) Fhase:288, (7) NEX: 1.00, and (8) Bandwith:31.25.

Volbrain Volumetry Report

The VolBrain system is an internet-based program that analyzes brain sMRI data automatically, reliably, and cantially. Axial T1 DICOM (Digital Imaging and Communications in Medicine) files were converted to the Neuroimaging Informatics Technology Initiative (NIFI-1) format. Whole brain volumetric analysis was performed by uploading compressed T1-weighted images in NIFTI format to the online "volBrain" MRI brain volumetric system. VolBrain created a PDF report that included an automatic MRI analysis of brain data and the two-sided volumes of the structures and volume information about total intracranial cavities. After an average of 12 min of processing time, volumetric measurements of white matter, gray matter, cerebrospinal fluid, cerebrum, cerebellum, nucleus caudatus, globus pallidus, putamen, nucleus accumbens, thalamus, hippocampus, and amygdala were obtained. The resulting volumes were statistically compared between groups and the possibility of volumetric differences was reviewed. A statistical comparison of the obtained data between the groups was obtained by proportioning the volumes of each case as right/left parts.

Statistical analysis

The SPSS 21.0 Statistical Package Program was used to evaluate the data. Descriptive analyses of categorical data were obtained, and the results were expressed as numbers and percentages. A chi-squared test (Fisher's Exact chi-squared test as needed) test was used for comparative evaluation of categorical data. Normal distribution eligibility of continuous data was evaluated with the Kolmogorov–Smirnov test. Mean and standard deviation values of the data that follow a normal distribution and median and quarters clearance values of the data that do not follow a normal distribution are given. For comparison of continuous data between binary groups, an independent T-test was used for data following a normal distribution, and Mann–Whitney U (MWU) test was applied to data that did not follow a normal distribution. A statistically significant *P*-value was accepted as < 0.05.

Results

In our study; volBrain results from 30 individuals, including 16 patient cases and 14 in the control group, were evaluated. No significant difference in terms of gender ($\chi 2$ [1, n = 30] = 0.117; $P = 0.732$), education level (2 [1, n = 30] = 0.002; $P = 0.961$])and marital status ($P = 0.596$, Fisher's exact test) were found (Table 1). However, both groups were found to be similar in terms of age ($P = 0.608$, MWU test). In our study, total brain and total white/gray matter volumes in addition to cerebellum, ventricle, nucleus caudatus, putamen, thalamus, globus pallidus, hippocampus, amygdala, and nucleus accumbens volumes were compared separately for right and left between case and control groups. In terms of these variables, no statistical difference was found between the case and control groups except for the right globus pallidus volume ($P = 0.008$, independent T-test), and the findings are summarized in Table 2. However, the right/left ratios of volumes for each brain region mentioned earlier were also compared between groups.

Significant differences between the case and control groups in terms of right/left ratios of cerebellum (P = 0.006, independent T-test) and nucleus caudatus (P = 0.028, MWU test) volumes were noted. The statistical analysis of the right/left ratios of the volumes of the brain regions is summarized in Table 3.

Table 1: Sociodemographic features of case and control groups

	Case (n=16) Median (IQR)	Control (n=14) Median (IQR)	*P*-value
Age (Years)	55.5 (31)	69 (33)	0.608[a]
	Case (n=16) Number (%)	Control (n=14) Number (%)	*P*-value
Gender			
Male	9 (56.25%)	7 (50%)	0.732[b]
Female	7 (43.75%)	7 (50%)	χ^2: 0.117
Education Level			
Below high school	9 (56.25%)	8 (57.14%)	0.961[b]
High school and above	7 (43.75%)	6 (42.86%)	χ^2: 0.002
Marital Status			
Married	11 (68.75%)	10 (71.43%)	0.596[c]
Other	5 (31.25%)	4 (28.57%)	

IQR: inter-quartile range, [a] Mann–Whitney U Test, [b] Chi-Squared Test, [c] Fisher's Exact Test

Table 2: Volumetric data of different brain structures in case and control groups

	Case (n=16) Mean (SD)	Median (IQR)	Control (n=14) Mean (SD)	Median (IQR)	*P*-value
WM Volume (cm^3)	539.98 (81.30)		521.74 (81.09)		0.847[a]
GM Volume (cm^3)	658.61 (114.84)		643.22 (73.5)		0.186[a]
Right Cerebrum Volume (cm^3)	526.6 (61.24)		514.29 (58.65)		0.879[a]
Left Cerebrum Volume (cm^3)	519.79 (59.13)		507.23 (57.46)		0.997[a]
Right Cerebellum Volume (cm^3)		63.88 (9.95)		60.65 (7.54)	0.423[b]
Left Cerebellum Volume (cm^3)		64.08 (8.99)		57.3 (8.84)	0.179[b]
Right Ventricle Volume (cm^3)		9.05 (9.78)		7.23 (32.26)	0.728[b]
Left Ventricle Volume (cm^3)		10.52 (7.49)		10.04 (31.87)	0.951[b]
Right Caudate Volume (cm^3)		3.3 (0.91)		3.47 (1)	0.240[b]
Left Caudate Volume (cm^3)	3.25 (0.5)		3.32 (0.48)		0.965[a]
Right Putamen Volume (cm^3)	3.85 (0.76)		3.44 (0.69)		0.921[a]
Left Putamen Volume (cm^3)	3.71 (0.85)		3.66 (0.63)		0.242[a]
Right Thalamus Volume (cm^3)	5.32 (1.24)		5.16 (0.76)		0.147[a]
Left Thalamus Volume (cm^3)	5.34 (1.46)		5.27 (0.84)		0.078[a]
Right GP Volume (cm^3)	0.98 (0.2)		0.92 (0.38)		0.008[a]
Left GP Volume (cm^3)	0.95 (0.32)		0.92 (0.3)		0.260[a]
Right Hippocampus Volume (cm^3)	3.64 (0.61)		3.82 (0.53)		0.781[a]
Left Hippocampus Volume (cm^3)	3.55 (0.69)		3.65 (0.37)		0.188[a]
Right Amygdala Volume (cm^3)	0.54 (0.25)		0.54 (0.18)		0.209[a]
Left Amygdala Volume (cm^3)	0.57 (0.26)		0.51 (0.2)		0.249[a]
Right NA Volume (cm^3)		0.3 (0.1)		0.29 (0.22)	0.790[b]
Left NA Volume (cm^3)		0.34 (0.06)		0.36 (0.14)	0.697[b]

SD: standard deviation, IQR: inter-quartile range, WM: white matter, GM: gray matter, GP: globus pallidus, NA: nucleus accumbens, [a] Independent T-Test, [b] Mann–Whitney U Test

Table 3: Asymmetry parameters of case and control groups

	Case (n = 16) Mean (SD)	Median (IQR)	Control (n = 14) Mean (SD)	Median (IQR)	*P*-value
Right/Left Cerebrum Ratio		1.01 (0.03)		1.01 (0.03)	0.759[a]
Right/Left Cerebellum Ratio	1.01 (0.03)		1.02 (0.08)		0.006[b]
Right/Left Ventricle Ratio		0.89 (0.28)		0.95 (0.34)	0.790[a]
Right/Left Caudate Ratio		0.96 (0.1)		1.03 (0.15)	0.028[a]
Right/Left Putamen Ratio		0.99 (0.09)		0.98 (0.17)	0.294[a]
Right/Left Thalamus Ratio		0.98 (0.14)		0.99 (0.09)	0.854[a]
Right/Left GP Ratio		1.01 (0.28)		1.06 (0.19)	0.552[a]
Right/Left Hippocampus Ratio	1.04 (0.1)		1.05 (0.09)		0.642[b]
Right/Left Amygdala Ratio		0.92 (0.2)		1.01 (0.33)	0.052[a]
Right/Left NA Ratio		0.86 (0.16)		0.94 (0.23)	0.525[a]

SD: standard deviation, IQR: inter-quartile range, WM: white matter, GM: gray matter, GP: globus pallidus, NA: nucleus accumbens, [a] Independent T-Test, [b] Mann–Whitney U Test

Discussion

In our study, the volumetric measurements (cm^3) of the brain regions and the right/left brain ratios in MDD patients were investigated using volBrain, which is a fully automated segmentation technique. Comparison results of the right/left nucleus caudatus and right/left cerebellum volume ratios were found to be statistically significant. When the total volumes of the brain regions and the volume measurements of each of the right and left parts were compared, it was found that only the right globus pallidus volume was larger compared to the control group. In a recent Enhancing Neuro-Imaging Genetics Through Meta-Analysis (ENIGMA) consortium study in which 2,540 MDD cases and 4,230 control patients were included from 32 data sets in which the volumes of brain regions were compared, the presence of structural brain asymmetries in MDD was investigated. Although that study had a fairly large sample size, no significant difference was found between cerebral cortical and subcortical volumes between groups in the ENIGMA study [8]. Similar to our comprehensive study in the literature, the brain region volume results of our study were similar to the ENIGMA consortium study except that the right globus pallidus volumes of the case group were larger than the control group. This finding is remarkable in terms of representing the suitability of the use of the volBrain system in MDB.

In the ENIGMA study, it was thought that direct comparison of the brain region volumes of the cases may have had a cumulative effect. For this purpose, the comparison of the right/left volume ratios of the brain regions in our study was also designed to reveal the case-specific asymmetry bias. In this context, the differences between the groups of right/left nucleus caudatus and cerebellum volume ratios are remarkable in our study. When our results were analyzed, it was found that the right/left nucleus caudatus and right/left cerebellum ratios of the case group were lower than those of the control group. These results reveal an asymmetry in these brain regions of the case group in which the right parts are smaller than the left ones. The lack of significant differences in the results of our direct volumetric comparisons can be explained by the fact that asymmetry is not secondary to shrinkage or growth, that is, it may be a structural feature. When the meta-analysis of the studies conducted with functional neuroimaging techniques in the literature was analyzed, it was shown that the bilateral

caudatus gave less response to reward stimuli in patients with MDD [6, 34]. Hypoactivation of the right caudate during the processing of positive stimuli in MDD patients has also been reported in previous studies [10]. A recent sMRI study indicated that the total caudate nucleus size is smaller in MDD patients compared to the control group; in addition, the right part of the caudate nucleus shrinks more than the left [12]. In the same study, it was also stated that further studies are needed to investigate inter-hemispheric imbalances, assuming shrinkage in the right caudate nucleus may be due to asymmetry in cortical and subcortical volumes in MDD [12]. MRI-based manual segmentation studies found different results consisting of no decrease or change in nucleus caudatus volumes in individuals with MDD compared to healthy subjects [35, 36]. Our study shows that no change in the nucleus caudatus volume between the groups could be found. Asymmetry was detected when comparing the right/left nucleus caudatus ratios between the groups.

Considering the recent increase in the number of studies examining the relationship between MDD and cerebellum, it is interesting that our study found a significant difference in the right/left cerebellum ratios between the case and control groups. Recent studies emphasize the importance of investigating the relationship between basal ganglia and cerebellum volumes in patients with/without MDD [21, 22, 37]. In this relationship, it is assumed that the basal ganglia and cerebellum affect the cortical activity separately by different thalamic pathways during the first period [38]. However new evidence of the existence of direct subcortical connections between these two structures, it is accepted that they have the capability of affecting motor, cognitive, and limbic functions together [22]. In the first study defining the structural bond between basal ganglion and cerebellum in non-human primates, it was shown that the dentate nucleus of the cerebellum projects to the intralaminar nuclei of the thalamus and then to the striatum and outer globus pallidus using the transneuronal viral tracing method accompanied by marking of the neurons in the dentate nucleus [39]. From this point of view, the results presenting the difference in the right/left cerebellum, nucleus caudatus ratios, and right globus pallidus volumes detected in our study may be important. Direct connections between the basal ganglia and the cerebellum suggest that these regions work together to modulate processes, such as motor control and emotion recognition or expression [40]. In addition, it has been frequently emphasized in recent studies that the basal ganglia and cerebellum have common effects in regulating and exhibiting response selection, and reward feedback [22, 40]. However, as our study showed, neuroimaging studies examining cortico–striatal–pallidal–thalamic circuits in MDD patients indicate the presence of abnormalities concerning these regions [41–43]. The abnormalities of the right globus pallidus and nucleus caudatus (one of the structures of corpus striatum) may reflect the relationship of cortico–sriatal–pallidal–thalamic circuits in patients with MDD, a finding that has been emphasized in previous research. In addition, showing the right/left asymmetry of the cerebellum in our study is thought to shed light on the possible relationship between these circuits and the cerebellum. It is important that our study is the first comprehensive study carried out with the volBrain application in MDD patients.

Limitations and strengths

Relatively small sample size, single-center conduct of the study, retrospective design, older age of the patients selected for the study, and confounding effects of drugs can be counted as limitations of this study; however, the use of a fairly new segmentation method can make this study valuable. This information will form an important publically available pipeline for MDD-related structure segmentation, and it is hoped that it will allow researchers to better analyze their data in an easy to use, yet accurate and efficient, manner. This process suggests that the proposed method can be readily applied under different research and clinical conditions although a much larger validation will be required. In addition, the use of a web-based fully automatic segmentation technique, which is accessible, can limit the differences that can be created by various fully automatic segmentation algorithms in addition to the differences in manual segmentation applications due to different raters.

Future cross-sectional multicenter studies should not include different segmentation techniques and MRI acquisition parameters. The challenge of multicenter research can be overcome by using web-based fully automated segmentation volumetry systems and the use of data containing the same standardized MRI acquisition parameters because it is easy for clinicians around the world to access web-based fully automated segmentation volumetry systems.

Conclusion

In conclusion, in line with our hypothesis, our study supported the notion of cortico–striatal–pallidal–thalamic circuit abnormalities in current MDD research and found that some regions in this phase may contain structural asymmetry. In addition, this study contributed to the literature by adding information about structural asymmetry in the cerebellum to the studies examining the relationship between cerebellum and MDD. From this point of view, the use of volBrain, which presents volumetric findings compatible with the literature related to MDD, is also promising. Research on fully automatic segmentation techniques could become the driving force behind fully understanding the biological foundations of MDD in the future. Successful implementation of Volbrain in our study suggests that Volbrain may be an important part of clinical applications in many other neuropsychiatric disorders in the near future.

References

1. Cizza G, Ronsaville DS, Kleitz H, Eskandari F, Mistry S, Torvik S, et al. Clinical subtypes of depression are associated with specific metabolic parameters and circadian endocrine profiles in women: The power study. PLoS ONE. 2012;7(1):1-9.
2. Jiang X, Shen Y, Yao J, Zhang L, Xu L, Feng R, et al. Connectome analysis of functional and structural hemispheric brain networks in major depressive disorder. Transl psychiatry. 2019;9:1-12.
3. Fang Y, Mao R. Introduction. In: Fang Y, editor. Depressive Disorders: Mechanisms, Measurement and Management. 1st ed. Springer Nature Singapore Pte Ltd.; 2019. p.1–19.
4. Masdeu JC. Neuroimaging in psychiatric disorders. Neurotherapeutics. 2011; 8:93–102.
5. Peng D, Yao Z. Neuroimaging Advance in Depressive Disorder. In: Fang Y, editor. Depressive Disorders: Mechanisms, Measurement and Management. 1st ed. Springer Nature Singapore Pte Ltd.; 2019. p.59–85.
6. Pizzagalli DA, Holmes AJ, Dillon DG, Goetz EL, Birk JL, Bogdan R, et al. Reduced caudate and nucleus accumbens response to rewards in unmedicated individuals with major depressive disorder. Am J Psychiatry. 2009;166:702–10.
7. Han KM, De Berardis D, Fornaro M, Kim YK. Differentiating between bipolar and unipolar depression in functional and structural MRI studies. Prog. Neuro-Psychopharmacol. Biol. Psychiatry. 2019;91:20–7.
8. De Kovel CGF, Aftanas L, Aleman A, Alexander-Bloch AF, Baune BT, Brack I, et al. No alterations of brain structural asymmetry in major depressive disorder: An ENIGMA consortium analysis. Am J Psychiatry. 2019;176:1039–49.

9. Pereira DM, Khan A. Brain Lateralization of Emotional Processing in Depression. In: Breznoscakova D, editor. Depression. IntechOpen; 2017;25–33.
10. Murrough JW, Collins KA, Fields J, DeWilde KE, Phillips ML, Mathew SJ, et al. Regulation of neural responses to emotion perception by ketamine in individuals with treatment-resistant major depressive disorder. Transl psychiatry. 2015;5:1-7.
11. Grieve SM, Korgaonkar MS, Koslow SH, Gordon E, Williams LM. Widespread reductions in gray matter volume in depression. NeuroImage Clin. 2013;3:332–9.
12. Choi KW, Han KM, Kim H, Kim A, Kang W, Kang Y, et al. Comparison of shape alterations of the thalamus and caudate nucleus between drug-naïve major depressive disorder patients and healthy controls. J Affect Disord. 2020;264:279–85.
13. Bruder GE, Stewart JW, Hellerstein D, Alvarenga JE, Alschuler D, McGrath PJ. Abnormal functional brain asymmetry in depression: Evidence of biologic commonality between major depression and dysthymia. Psychiatry Res. 2012;196:250–4.
14. Zuo Z, Ran S, Wang Y, Li C, Han Q, Tang Q, et al. Asymmetry in cortical thickness and subcortical volume in treatment-naïve major depressive disorder. NeuroImage Clin. 2019;21:1–6.
15. Rashid B, Calhoun V. Towards a brain-based predictome of mental illness. Hum Brain Mapp. 2020;41:3468–535.
16. Bruder GE, Stewart JW, McGrath PJ. Right brain, left brain in depressive disorders: Clinical and theoretical implications of behavioral, electrophysiological and neuroimaging findings. Neurosci biobehav rev. 2017;78:178–91.
17. Andreescu C, Butters MA, Begley A, Rajji T, Wu M, Meltzer CC, et al. Gray matter changes in late life depression - A structural MRI analysis. Neuropsychopharmacology. 2008;33:2566–72.
18. Zhang H, Li L, Wu M, Chen Z, Hu X, Chen Y, et al. Brain gray matter alterations in first episodes of depression: A meta-analysis of whole-brain studies. Neurosci Biobehav Rev. 2016;60:43–50.
19. Bora E, Fornito A, Pantelis C, Yücel M. Gray matter abnormalities in Major Depressive Disorder: A meta-analysis of voxel based morphometry studies. J Affect Disord. 2012;138:9–18.
20. Pizzagalli DA. Frontocingulate dysfunction in depression: Toward biomarkers of treatment response. Neuropsychopharmacology. 2011;36:183–206.
21. Minichino A, Bersani FS, Trabucchi G, Albano G, Primavera M, Chiaie RD, et al. The role of cerebellum in unipolar and bipolar depression: A review of the main neurobiological findings. Riv Psichiatr. 2014;49:124–31.
22. Pierce JE, Péron J. The basal ganglia and the cerebellum in human emotion. Soc Cogn Affect Neurosci. 2020;15:599–613.
23. Escalona PR, Early B, McDonald WM, Doraiswamy PM, Shah SA, Husain MM, et al. Reduction of cerebellar volume in major depression: A controlled MRI study. Depression. 1993;1:156–8.
24. Peng J, Liu J, Nie B, Li Y, Shan B, Wang G, et al. Cerebral and cerebellar gray matter reduction in first-episode patients with major depressive disorder: A voxel-based morphometry study. Eur J Radiol. 2011;80:395–9.
25. Akudjedu TN, Nabulsi L, Makelyte M, Scanlon C, Hehir S, Casey H, et al. A comparative study of segmentation techniques for the quantification of brain subcortical volume. Brain imaging behav. 2018;12:1678–95.
26. Doring TM, Kubo TTA, Cruz LCH, Juruena MF, Fainberg J, Domingues RC, et al. Evaluation of hippocampal volume based on MR imaging in patients with bipolar affective disorder applying manual and automatic segmentation techniques. J Magn Reson Imaging. 2011;33:565–72.
27. Van Erp TG, Hibar DP, Rasmussen JM, Glahn DC, Pearlson GD, Andreassen OA, et al. Subcortical brain volume abnormalities in 2028 individuals with schizophrenia and 2540 healthy controls via the ENIGMA consortium. Mol Psychiatry. 2016;21:547–53.
28. Franke B, Stein JL, Ripke S, Anttila V, Hibar DP, van Hulzen KJE, et al. Schizophrenia Working Group of the Psychiatric Genomics Consortium: ENIGMA Consortium, O'Donovan MC, Thompson PM, Neale BM, Medland SE, Sullivan PF. Genetic influences on schizophrenia and subcortical brain volumes: Large-scale proof of concept. Nat Neurosci. 2016;19:420–31.
29. Hannoun S, Tutunji R, El Homsi M, Saaybi S, Hourani R. Automatic Thalamus Segmentation on Unenhanced 3D T1 Weighted Images: Comparison of Publicly Available Segmentation Methods in a Pediatric Population. Neuroinformatics. 2019;17:443–50.
30. Manjon J V, Coupe P. volBrain: An Online MRI Brain Volumetry System. Front neuroinform. 2016;10:1-14.
31. Næss-Schmidt E, Tietze A, Blicher JU, Petersen M, Mikkelsen IK, Coupé P, et al. Automatic thalamus and hippocampus segmentation from MP2RAGE: comparison of publicly available methods and implications for DTI quantification. Int J Comput Assist Radiol Surg. 2016;11:1979–91.
32. Hedderich DM, Spiro JE, Goldhardt O, Kaesmacher J, Wiestler B, Yakushev I, et al. Increasing Diagnostic Accuracy of Mild Cognitive Impairment due to Alzheimer's Disease by User-Independent, Web-Based Whole-Brain Volumetry. J Alzheimers Dis. 2018;65:1459–67.
33. Özkürkçügil A, Aydemir Ö, Yıldız M, Esen Danacı A, Köroğlu E. DSM-IV Eksen I Bozuklukları için Yapılandırılmış Klinik Görüşmenin Türkçeye Uyarlanması ve Güvenilirlik Çalışması. İlaç ve Tedavi Dergisi. 1999;12:233–6.
34. Diener C, Kuehner C, Brusniak W, Ubl B, Wessa M, Flor H. A meta-analysis of neurofunctional imaging studies of emotion and cognition in major depression. NeuroImage. 2012;61:677–85.
35. Lacerda AL, Nicoletti MA, Brambilla P, Sassi RB, Mallinger AG, Frank E, et al. Anatomical MRI study of basal ganglia in major depressive disorder. Psychiatry Res Neuroimaging. 2003;124:129–40.
36. Parashos IA, Tupler LA, Blitchington T, Krishnan KRR. Magnetic resonance morphometry in patients with major depression. Psychiatry Res Neuroimaging. 1998;84:7–15.
37. Bostan AC, Strick PL. The basal ganglia and the cerebellum: Nodes in an integrated network. Nat Rev Neurosci. 2018;19:338–50.
38. Middleton FA, Strick PL. Basal ganglia and cerebellar loops: Motor and cognitive circuits. Brain Res Rev. 2000;31:236–50.
39. Hoshi E, Tremblay L, Féger J, Carras PL, Strick PL. The cerebellum communicates with the basal ganglia. Nat Neurosci. 2005;8:1491–3.
40. Caligiore D, Arbib MA, Miall RC, Baldassarre G. The super-learning hypothesis: Integrating learning processes across cortex, cerebellum and basal ganglia. Neurosci Biobehav Rev. 2019;100:19–34.
41. Vang FJ, Ryding E, Träskman-Bendz L, van Westen D, Lindström MB. Size of basal ganglia in suicide attempters, and its association with temperament and serotonin transporter density. Psychiatry Res Neuroimaging. 2010;183:177–9.
42. Gosnell SN, Velasquez KM, Molfese DL, Molfese PJ, Madan A, Fowler JC, et al. Prefrontal cortex, temporal cortex, and hippocampus volume are affected in suicidal psychiatric patients. Psychiatry Res Neuroimaging. 2016;256:50–6.
43. Monkul ES, Hatch JP, Nicoletti MA, Spence S, Brambilla P, Lacerda AL, et al. Fronto-limbic brain structures in suicidal and non-suicidal female patients with major depressive disorder. Mol Psychiatry. 2007;12:360–6.

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