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Research Article

Volumetric Evaluation of Substantia Nigra in Major Depressive Disorder Using Atlas-Based Method

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Abstract

Aim: The substantia nigra pars compacta (SNc), a vital part of the brain that produces dopamine, is being closely studied due to its potential role in the monoamine hypothesis, which aims to explain the causes of Major Depressive Disorder (MDD). Dopamine, a chemical messenger in the brain, is linked to the monoamine hypothesis, suggesting that imbalances in these chemicals may contribute to MDD. This study aimed to calculate volumetric changes in the substantia nigra (SN), using brain magnetic resonance imaging (MRI) in individuals diagnosed with MDD.

Material and Method: Sixty-six participants, comprising 33 individuals diagnosed with MDD (mean age=44.30±13.98 years) and 33 healthy individuals (mean age=46.27±14.94 years), were recruited from the university hospital psychiatry outpatient clinic. In the MDD group, there were 15 male participants (45%) and 18 female participants (55%). The healthy control group consisted of 28 males (84.8%) and 5 females (16.2%). Potential confounding factors, such as underlying chronic diseases, were ruled out by the clinician through a thorough examination of the patient's medical history, ensuring the study outcomes were not influenced. Three-dimensional brain MRI scans were conducted using a 1.5 Tesla MRI scanner. Volumes of the SN and midbrain were automatically computed using MRIStudio, an atlas-based image analysis program.

Results: Statistically significant higher volumes were observed in the right SN in the MDD group compared to controls (0.146±0.045 cm^3 vs. 0.122±0.035 cm^3, p=0.02, p<0.05). The ratio of SN to midbrain volume was higher in MDD patients on both sides, with a 22.4% higher value on the right side and a 12.7% higher on the left side relative to controls (p=0.002 for the right, p=0.01 for the left; p<0.05). Moreover, a negative correlation between left and right SN volumes and age was identified in the MDD group (p=0.01 for the left, p=0.05 for the right side; p<0.05).

Conclusion: Our study revealed an increase in SN volume in MDD patients. Identifying volumetric discrepancies in brain regions responsible for dopamine release could hold significant value in elucidating the underlying causes of the disease and guiding treatment strategies.

Keywords: Dopamine, magnetic resonance imaging, major depressive disorder, substantia nigra

INTRODUCTION

Major Depressive Disorder (MDD) has emerged as a pervasive public health issue, severely compromising overall well-being worldwide (1). Global estimates from the 2017 World Health Organization (WHO) report indicate that MDD affects over 300 million individuals, with suicide attempts being a leading cause of mortality, accounting for approximately 800,000 deaths each year (2). MDD's impact on public health surpasses that of other prevalent conditions such as coronary heart disease, rheumatoid arthritis, and diabetes mellitus (3). A study reports a 12-month prevalence of 6.6% and a lifetime prevalence of 16.2% for MDD (4). Given its significant prevalence and detrimental effects, effective MDD treatment is of paramount importance for public health. A more comprehensive understanding of MDD's pathophysiology and associated morphological changes can significantly enhance diagnosis and treatment strategies in clinical practice (5) Therefore identifying structural findings associated with the monoamine hypothesis, a widely accepted theory regarding MDD's pathophysiology, is crucial (6).

The monoamine hypothesis proposes that a central neurophysiological factor contributing to MDD is a

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reduction in the levels of monoaminergic transmission (serotonin, norepinephrine, and/or dopamine) within the central nervous system (6). Based on this hypothesis, antidepressants, particularly monoamine reuptake inhibitors, have been developed and are extensively used in clinical practice (7). Despite extensive research efforts, direct evidence supporting the monoamine hypothesis remains largely inconclusive (8). Therefore, further research is needed to strengthen the evidence supporting the monoamine hypothesis.

Dopamine, one of the monoamine neurotransmitters, plays a crucial role in various functions of the central nervous system, including regulation of movement, cognitive executive functions, and emotional limbic activity (9). Alterations in dopaminergic pathways have been shown to affect both locomotor activity and cognitive functions (10,11). The midbrain houses approximately 90% of the brain's dopamine-producing neurons. Within the midbrain, the substantia nigra pars compacta (SNc) and ventral tegmental area host the majority of these dopaminergic neurons (12). The SNc, recognized as a dopaminergic nucleus essential for modulating motor movements and reward functions within the basal ganglia circuitry, plays a pivotal role (9).

A study reported an instance in which erroneous deep brain stimulation of the SN resulted in a reversible severe depressive episode (13). Numerous studies have demonstrated a correlation between volumetric changes in the SN observed in various neuropsychiatric disorders and brain functions (14,15).

In our study, we aimed to evaluate substantia nigra (SN) volume differences in MDD patients using brain magnetic resonance imaging (MRI) and an atlas-based automated volumetric measurement method. We believe that assessing volumetric differences in the SN, a critical center for dopamine synthesis, will contribute to elucidating the etiology of MDD.

MATERIAL AND METHOD

Participants

Sixty-six participants were enrolled in our study, including 33 patients diagnosed with MDD (mean age=44.30±13.98 years) and 33 healthy individuals (mean age=46.27±14.94 years), who were recruited from the university hospital psychiatry outpatient clinic. The study comprised 15 male participants (45%) and 18 female participants (55%) in MDD group. 28 males (84.8%) and 5 females (16.2%) were included in healthy control group. No gender-specific analyses were conducted due to asymmetric sex ratios in the study groups. All participants underwent assessment using the Hamilton Depression Rating Scale (HAM-D) and the Hamilton Anxiety Rating Scale (HAM-A).

The clinical assessments in this study were conducted following the guidelines outlined by the American Psychiatric Association (APA) clinical practice guidelines. Participants underwent clinical psychiatric assessment were subsequently categorized into two groups: a control group comprising individuals with no diagnosed mental health conditions, and a patient group consisting of individuals diagnosed with MDD.

Inclusion criteria for MDD patients were the ability to use their right hand, the absence of any chronic illnesses, and no history of bipolar disorder, psychosis, or other psychiatric disorders in the patient or their first-degree relatives. Exclusion criteria for the healthy control group included a history of any psychiatric disorders, any neurological diseases, a cerebral trauma history resulting in a coma lasting more than five minutes, left-handedness, and the presence of individuals with psychotic or bipolar disorders among their first-degree relatives. No exclusions were made from the healthy group; all participants initially categorized as healthy remained part of the analysis throughout the study.

Ethical approval for this study was obtained from Çanakkale 18 Mart Universty Ethical Committee (Approval No: 2013/75, dated 09/10/2013), and written informed consent was obtained from all participants.

MRI Protocol

MRI scans were acquired using a 1.5 Tesla Magnetic Resonance unit (Philips Ingenia, Netherlands, 2013). For volumetric measurements, we utilized images acquired in the axial plane using a T1-weighted 3D multiplanar turbo spin-echo sequence. The imaging parameters included voxel dimensions of 1x1x1 mm, a Repetition Time (TR): of 7.0 ms, an Echo Time (TE): of 3.4 ms, a Field of View (FoV): of 256x240, a Matrix: of 256x216, a slice thickness of 0.9 mm, and no gap.

Volumetric Calculation with Atlas-Based Method

The volume of relevant brain structures was automatically calculated using MRIStudio, an atlas-based image analysis software developed by H. Jiang and S. Mori at Johns Hopkins University (16). The MRIStudio program consists of DTIStudio, DiffeoMap, and ROIEditor software. Images were processed using DTIStudio and MRIcro to separate bone structures. DiffeoMap aligned images with a template, and the subject image was saved as "updated_maskT1." The resulting data were sent for analysis. Each participant's image was linearly and nonlinearly transformed using large deformation diffeomorphic metric mapping to match single-participant skull-stripped templates produced by Johns Hopkins University (17). The DiffeoMap software aligned the template image ("Updated_maskT1") and the subject image ("JHU_MNI_SS_BPM_Typell_V2.1"). The ROIEditor program obtained volumes by overlaying "Updated_Lddmmposthmap.img0" onto MaskT1, with results saved as "roi statistics" in the working file. After normalizing the MR images, the ROIEditor software was employed to automatically divide the brain into 160-180 anatomical structures and calculate their volumes (Figure 1). Procedures for calculating the volumes of brain regions using MRIStudio have been previously described in other studies (16,18).

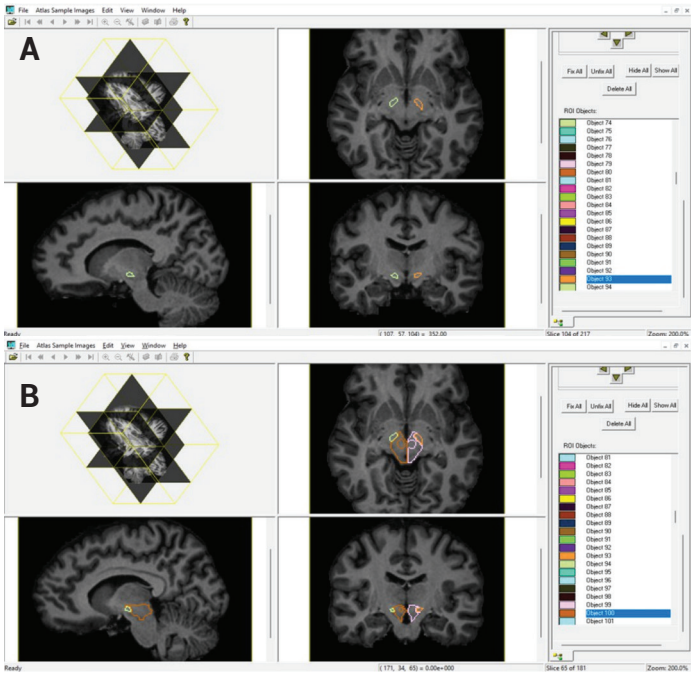

Figure 1. A. Identification of the substantia nigra on normalized images using ROIEditor, **B.** Identification of the midbrain areas on normalized images using ROIEditor

Statistical Analysis

All volumetric data were expressed as mean±standard deviation (SD). The Shapiro-Wilk test was used for normality analysis of continuous variables. Since continuous variables met the assumption of normality, independent samples t-tests were used in univariate analyses. Similarly, Pearson correlation analysis was used in correlation analyses as continuous variables met the assumption of normality. Results with a p-value less than 0.05 were considered statistically significant.

RESULTS

Sociodemographic data for both the patient and control groups are summarized in Table 1. Volumetric data for the assessed brain structures are presented in Table 2. Patients with MDD exhibited significantly higher right SN volume (0.146±0.045 cm³ vs. 0.122±0.035 cm³, p=0.02, p<0.05) (Figure 2), HAM-D, and HAM-A scores compared to the control group (p=0,001 for both HAM-D and HAM-A, p<0.05) (Figures 3). We also noticed that the SN volume-to-midbrain volume ratio (SNVR) statistically increased to 22.4% on the right side (p=0.002, p<0.05) (Figure 4) and to 12.7% on the left side (p=0.01, p<0.05) (Figure 4) in MDD patients respect to the control group. Correlation analysis revealed a statistically significant negative correlation between age and the volumes of both the left and right SN respectively in the MDD group (p=0.015, p=0.05; p<0.05) (Table 3).

Table 1. Demographic data and clinical characteristics of MDD patients and healthy controls

	Controls (Mean±SD)	MDD (Mean±SD)
Age (year)	46.27±14.94	44.30±13.98
Female/male	(18/15)	(28/5)
HAM-D score	2.30±1.31	17.48±6.03*
HAM-A score	3.00±1.15	17.58±6.31*

MDD: major depressive disorder, HAM-D: Hamilton rating scale for depression, HAM-A: Hamilton rating scale for anxiety, SD: standard deviation. * Both HAM-D and HAM-A scores were higher in MDD group significantly in comparison to HC (p=0.001, p<0.05)

Tablo 2. Mean volumes of brain regions in MDD and control groups

Brain regions	Control (cm³) Mean±SD	MDD (cm³) Mean±SD	P value
LEFT SN	0.149±0.043	0.164±0.036	0.144
RIGHT SN	0.122±0.035	0.146±0.045	**0.023**
LEFT MB	2.648±0.382	2.611±0.446	0.791
RIGHT MB	3.169±0.493	3.102±0.522	0.598
TOTAL MB	5.817±0.860	5.713±0.950	0.679
LEFT SNVR	0.056±0.011	0.063±0.011	**0.010**
RIGHT SNVR	0.038±0.008	0.047±0.013	**0.002**

MDD: major depressive disorder, SD: standard deviation, SN: substantia nigra, MB: midbrain, SNVR: substantia nigra volume ratio

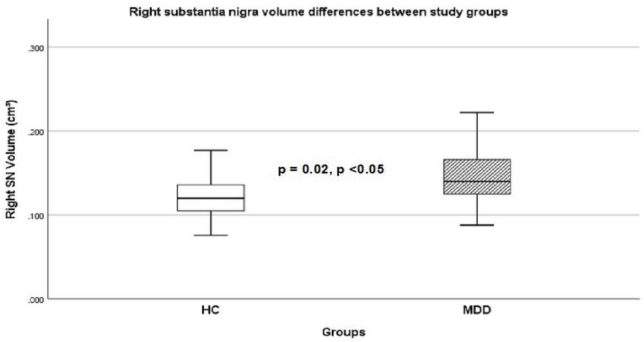

Figure 2. Box plot showing right side substantia nigra volume differences between MDD group and healthy controls. MDD: Major depressive disorder, SN: Substantia nigra, HC: Healthy controls

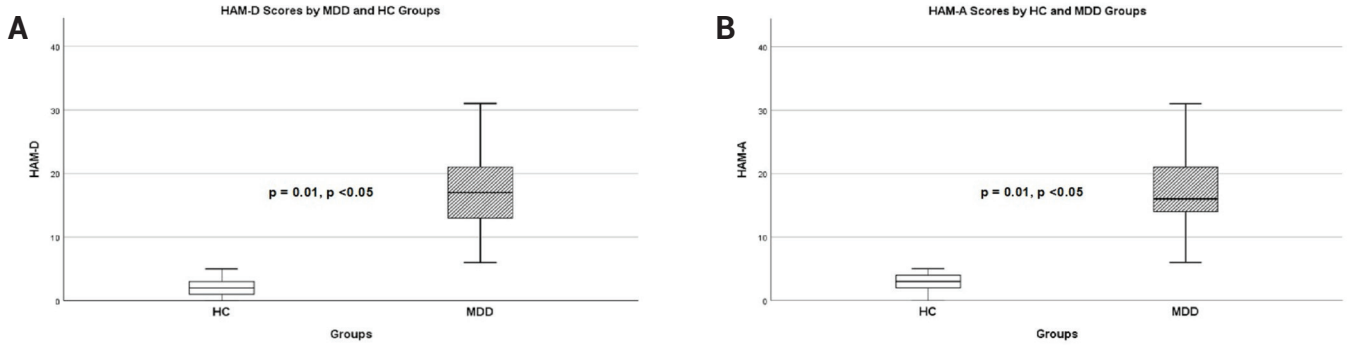

Figure 3. A. Box plot of HAM-D score differences between MDD group and healthy controls, **B.** Box plot of HAM-A score differences between MDD group and healthy controls. MDD: major depressive disorder, HC: healthy controls, HAM-D: Hamilton Rating Scale for depression, HAM-A: Hamilton Rating Scale for anxiety

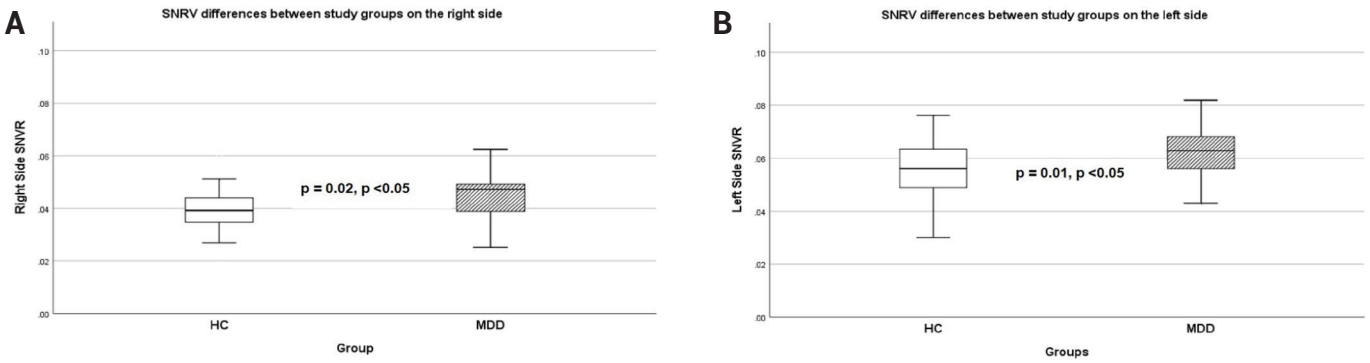

Figure 4. A. Box plot of right SN to midbrain volume ratio (SNVR) differences between MDD group and healthy controls, **B.** Box plot of left SN to midbrain volume ratio (SNVR) differences between MDD group and healthy controls, HC: healthy controls, MDD: major depressive disorder, SN: substantia nigra, SNV: substantia nigra volume ratio

Table 3. Correlation between average volumes of brain regions in the MDD group and age, HAM-D, and HAM-A scores

		Left SN	Right SN	Left MB	Right MB	Total MB	Left SNVR	Right SNVR
Age	**r**	-0.422	-0.343	-0.260	-0.271	-0.271	-0.285	-0.208
	p	**0.015**	**0.050**	0.144	0.128	0.127	0.108	0.246
HAM-D	**r**	0.187	-0.124	0.296	0.210	0.255	-0.064	-0.264
	p	0.296	0.491	0.094	0.240	0.152	0.722	0.138
HAM-A	**r**	0.020	-0.193	0.152	0.050	0.099	-0.101	-0.245
	p	0.914	0.281	0.400	0.781	0.585	0.577	0.169

MDD: major depressive disorder, HAM-D: Hamilton rating scale for depression, HAM-A: Hamilton rating scale for anxiety, SN: substantia nigra, MB: midbrain, SNVR: substantia nigra volume ratio

DISCUSSION

MDD is a clinically heterogeneous, multifactorial condition. In our study, we found an increase in the volume of the right SN and the bilateral SN volume to midbrain ratio in patients with MDD. The identification of these alterations shows potential for refining diagnosis and advancing targeted therapeutic interventions in the context of MDD (19,20). The SN is a crucial component of the reward pathway, termed as the limbic-cortical-striatal-pallidal-thalamic circuit. Numerous studies have indicated volumetric differences in brain regions associated with this pathway in MDD, suggesting that functional and volumetric alterations in these regions could play a significant role in MDD pathogenesis (21-24). Furthermore, several neuroimaging studies have shown volume reductions in prefrontal cortex areas, anterior cingulate cortex, hippocampus, amygdala, and subcortical brain regions such as the basal ganglia in MDD patients (25,26).

A thorough review of the literature revealed prior studies directly investigating SN volume in Parkinson's disease but found a scarcity of such studies for MDD (27-32). However, volumetric or pathophysiological changes and dopaminergic dysregulation in the SN have been reported in several neuropsychiatric disorders. Gao et al. observed reductions in bilateral SN volume and decreased functional connectivity in the left SN in patients with traumatic brain injury, emphasizing the association of these structural and functional changes with increased anxiety and depressive symptoms (14). Kempton et al. found an increase in SN volume in patients with bipolar disorder (33). Moreover, in a study conducted on schizophrenia patients, an increase in the size of SN dopaminergic neurons' nucleoli and nuclei was demonstrated (27). In addition, the prevalence of depression accompanying schizophrenia was found to be 28.6% in a meta-analysis (34). The changes in SN volume observed in various neuropsychiatric disorders are not only consistent with our findings but also support the hypothesis that volumetric and functional alterations in the SN and its connected brain regions are associated with depressive symptoms.

In addition to studies measuring the volumes of brain regions, positron emission tomography (PET) imaging studies have reported a significant decrease in dopamine transporter activity in patients with MDD compared to healthy subjects, suggesting a reduction in dopaminergic neurotransmission, a key neurochemical mechanism implicated in the pathophysiology of depression (35,36). Based on ex vivo immunohistochemical measurements in the human brain, approximately 68% of all dopaminergic neurons identified in the midbrain are in the SNc, and 12% are in the ventral tegmental area (37). Dubol et al. found that individuals with depression have lower levels of dopamine transporters in upper midbrain areas, including the SN, ventral tegmental area, and the right putamen region. They suggested that the decrease in dopamine transporter levels could result from impaired dopaminergic function, structural changes in dopaminergic neurons, or both (35). Another study associated hyperintensity in the SN observed in patients with MDD with functional impairment in the nigrostriatal dopaminergic system (29). Therefore, alterations in dopaminergic neuron morphology and function in MDD may underlie the volumetric and intensity changes observed in the SN, suggesting a role for SN

structural plasticity in the pathophysiology of depression.

Several meta-analyses have emphasized that variations in brain region volumes among individuals with MDD may be influenced by disease progression, the age at which the disease manifests, and the administration of antidepressant medication (21,38). In MRI investigations addressing the timing of disease initiation in MDD, reductions in gray matter volume were noted in early-onset cases within the right fusiform gyrus, right middle temporal gyrus, and right posterior cingulate cortex. Conversely, augmented gray matter volume was discerned in the right middle occipital gyrus and left middle temporal gyrus in instances of late-onset (39). Another examination involving MDD patients with a later onset revealed heightened thickness in the right prefrontal cortex and orbitofrontal cortex compared to those with an early onset. Moreover, onset before the age of 30 is considered early onset in the literature (40). Considering that our study's average participant age exceeded 30, and an elevation in SN volume was noted in the patient cohort, our findings align with these established patterns. Observed alterations in volume associated with the age at which the disease begins could stem from distinct pathological mechanisms or represent compensatory responses.

A limited sample size and the unavailability of measures for dopaminergic neurotransmission activity constrain the limitations of our study.

CONCLUSION

In conclusion, the investigation of structural and functional alterations within the SN in MDD via neuroimaging methods holds potential utility for clinicians in MDD diagnosis and disease progression assessment. Longitudinal neuroimaging inquiries can shed light on the temporal dynamics of SN volume changes, elucidating whether these changes are constant or progressive. Additionally, such studies can elucidate how SN volume alterations correlate with variables such as antidepressant medication use, disease severity or patient age. The detailed analysis of the SN's structural changes in MDD is poised to play a significant role in understanding the fundamental pathogenesis of the disease.

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Conflict of interest: *The authors have no conflicts of interest to declare.*

Ethical approval: *Ethical approval was taken from Çanakkale 18 Mart University, Non-interventional Clinical Researchers Ethical Committee (2013/75).*

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