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RESEARCH ARTICLE

Enlarged basal ganglia in drug-naïve patients with first-episode psychosis immediately upon symptom onset

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ABSTRACT

Objective: The basal ganglia play a crucial role in understanding the pathobiology of psychosis. While alterations in the basal ganglia are known to occur in psychosis, the timing of these alterations relative to the emergence of symptoms is not yet understood. This study aimed to investigate whether there is a change in the basal ganglia in drug-naïve first-episode psychosis (FEP) patients seeking hospital care immediately upon symptom emergence.

Method: Seventy-one drug-naïve FEP patients who presented to the psychiatry outpatient clinic within the first month of symptom emergence were diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5). Along with 47 healthy controls (HC), they were included in the study, totaling 118 participants (64 males, 54 females). T1-weighted images were acquired through magnetic resonance imaging, and basal ganglia volume was measured using volBrain software. Symptoms were assessed using the Positive and Negative Syndrome Scale (PANSS) by an experienced psychiatrist.

Results: The volumes of the right (R) and left (L) striatum, R- and L-caudate (CAU), and R- and L- substantia nigra (SN) were found to be higher in FEP patients compared to HCs. While the volume of the L-putamen was higher, the volumes of the L-globus pallidus (GP) and L-nucleus accumbens (NAcc) were smaller in FEP compared to HCs. No significant correlation was found between volume measurements and PANSS scores. The R-CAU, L-CAU, R-Striatum, L-Striatum, L-Putamen, L-NAcc, R-GP, and L-SN were found to significantly differentiate psychosis in a univariate logistic regression model.

Conclusion: From the initial stage of psychosis, even upon the immediate emergence of symptoms, the basal ganglia are affected and may play a role in the pathogenesis of the disorder.

Keywords: Basal ganglia, first-episode psychosis, magnetic resonance imaging, schizophrenia

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INTRODUCTION

Schizophrenia (SZ) is a progressive, chronic mental disorder affecting approximately 1% of the population, usually first identified during late adolescence or young adulthood (1). Schizophrenia is associated with significant modifications in brain structure, including changes in the shape of the cortex (2), reductions in subcortical volume (2), and adjustments in white matter (3), resulting in disruptions in structural connectivity (4). The basal ganglia, a group of subcortical brain structures located in the telencephalon, diencephalon, and mesencephalon, play a pivotal role in motor, cognitive, and affective functions (5). Research has traditionally focused on motor and movement disorders associated with the basal ganglia, such as Parkinson's and Huntington's diseases. However, the role of the basal ganglia in psychiatric disorders has garnered attention, particularly with discoveries concerning its involvement in cognitive and affective functions (6).

The basal ganglia have been implicated in the pathogenesis of SZ due to the high levels of D2 receptors. Additionally, they are thought to contribute to the disease's development through their involvement in emotional and cognitive functions via the cortico-thalamic-striatal-cortical circuit, where significant impairments of these functions are observed in SZ (7) (Fig. 1). The nucleus accumbens (NAcc), a basal ganglion located in the ventral striatal area, is regarded as the brain's reward center. Its role in SZ has been emphasized through its association with the development of negative symptoms (8). Investigating dysfunctions in the basal ganglia is important due to their significant role in SZ pathogenesis and because they are targeted by antipsychotics.

Previous studies have underscored the importance of the basal ganglia in understanding SZ's pathophysiology (9). While some research has shown that patients with SZ exhibit markedly decreased activation in the basal ganglia compared to healthy controls across various task domains, other studies have identified increased functional integration in the caudate nucleus (10). In a meta-analysis involving 2,028 patients with SZ and 2,540 controls, larger volumes of the pallidum and lateral ventricles were detected, alongside reductions in the size of the hippocampus, amygdala, thalamus, and accumbens in SZ patients compared to controls (11). However, the landscape is further complicated by several studies on first-episode and chronic psychosis that have reported conflicting results regarding basal ganglia volumes, ranging from increases to decreases and no significant changes (12–14). These inconsistencies underscore the need for further investigation, particularly concerning changes within the basal ganglia in SZ.

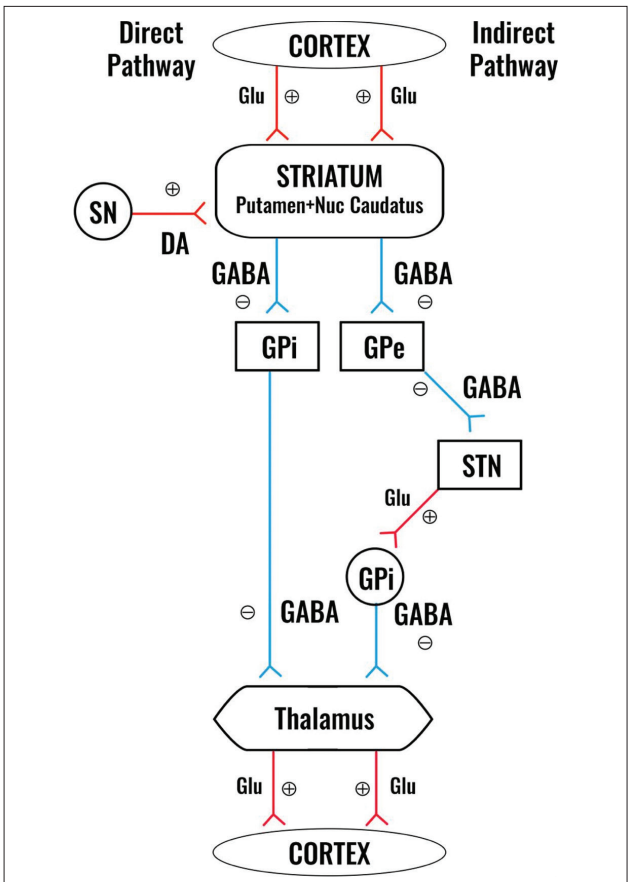

Figure 1. The working principle of basal ganglia.
Glu: Glutamate, DA: Dopamine, Gpi: Globus Pallidus interna, Gpe: Globus pallidus externa, SN: Substantia nigra, STN: Subthalamic nucleus.

Our study aims to bridge this gap by examining whether changes in the basal ganglia occur in drug-naïve patients with first-episode psychosis (FEP) who seek hospital care immediately upon symptom emergence. Adopting a distinct approach, our research explores the hypothesis that volumetric alterations in the basal ganglia manifest at the very onset of psychosis, precisely when symptoms first appear. This unique temporal window provides a valuable opportunity to investigate basal ganglia pathology at its earliest stages, free from the potential confounding effects of chronic antipsychotic medication use and disease progression. By concentrating on patients experiencing their first episode of psychosis, we aim to identify potentially distinct volumetric changes specific to this initial stage. This method has the potential to unveil crucial insights into the basal ganglia's role at the onset of the disease process.

METHODS

Participants

The study enrolled 71 drug-naïve patients with FEP who presented to the psychiatry outpatient clinic of Bakirkoy Prof. Mazhar Osman Training and Research Hospital for Psychiatry, Neurology and Neurosurgery (Istanbul, Turkiye) within the first month following the immediate onset of symptoms and were diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5). In this study, FEP was defined as the first occurrence of psychotic symptoms (e.g., delusions, hallucinations, disorganized thinking/behavior) in an individual's life, coinciding with their initial treatment contact (15). A neurologist evaluated all patients to exclude potential organic causes.

The control group comprised 47 healthy controls (HC) matched with the patient group by age, gender, and body mass index (BMI). HCs were recruited from individuals undergoing administrative procedures at the clinic or hospital staff undergoing routine checks under occupational health and safety regulations. Factors such as smoking habits and BMI levels were considered due to their impact on the total brain volume. All participants were between the ages of 18-50 years, with a BMI between 18 and 25. They were literate and had no known mental disabilities that would prevent their participation in the study. Furthermore, none had a diagnosis of any chronic systemic or neuropsychiatric diseases (relevant to the HC group only), nor did they have a personal or family history of neurodegenerative disorders. Additionally, participants did not use any drugs. Those diagnosed with substance-alcohol use according to DSM-5 criteria were excluded from the study. Urine tests were conducted on all participants to ensure and exclude any potential incidence of substance or alcohol abuse. The sample size was determined by evaluating the effect size as 0.4, the α-error as 0.05, power as 0.85, and using G*Power v. 3.1.9.2.

All participants were informed about the study procedures before the study began, and written consent was obtained. Only those who agreed to participate in the study were included in the final cohort. Ethical approval, in accordance with the World Medical Association (WMA) Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects, revised in 2013, was obtained from Hamidiye Ethics Committee (IRB Date/Number: 13 May 2022 - 22/275).

Study Procedure

Patients with FEP and HCs who met the study's inclusion criteria were referred to the research team by their physicians. After being informed about the study, both the FEP patients and the HCs provided written informed consent to participate. Subsequently, all participants completed sociodemographic and clinical data forms. Lastly, brain Magnetic Resonance Imaging (MRI) scans were obtained for all participants.

Evaluation Instruments

A sociodemographic data form was used to collect information on age, gender, educational level, marital status, smoking habits, and income level from both patients and control groups. The severity of symptoms in FEP patients was comprehensively evaluated using the Positive and Negative Syndrome Scale (PANSS), which was administered by an experienced clinician during the patient examination. This 30-item scale, which assesses symptom severity on a 7-point scale, includes three major subscales: Positive Symptoms (such as delusions, hallucinations, and disorganized speech), Negative Symptoms (including blunted affect, avolition, and social withdrawal), and General Psychopathology (covering additional symptoms and overall illness severity) (16). The adoption of PANSS, a reliable and extensively validated tool for assessing SZ, strengthens the study's findings by providing a comprehensive and standardized measure of symptom severity in FEP patients (16).

MRI Acquisition

MRI scans of the patients were performed using a 1.5T MRI device (Magnetom AERA, Siemens, Erlangen, Germany). High-resolution T1-weighted magnetization prepared rapid gradient echo (MPRAGE) images that encompassed the entire brain were analyzed. Each scan consisted of 176 slices with an isotropic voxel size of 1 mm^3, ensuring precise spatial resolution in all dimensions. The field of view (FOV) was set at 256 x 256 mm, corresponding to the matrix dimensions. Specified sequences were employed, leveraging over one year of data acquisition (176 slices, FOV=256 x 256, 1 mm isotropic voxels, TR=5.8 ms, TE=3.3 ms).

Volumetric Analysis

All MRI data were processed using volBrain, a web-based multi-atlas tool designed for the automated segmentation and quantitative volumetric analysis of the brain (17). VolBrain utilizes brain atlases stored on its cloud platforms to automatically estimate

Table 1: Comparison of sociodemographic and clinical data of patients with FEP and healthy controls (Mean±SD)

	Healthy Controls (n=47)	Patients with FEP (n=71)	df	p
Age	31.60±8.2	30.90±8.5	84	0.21
Gender (%)	Male: 24 (51%)	Male: 40 (56.3%)	1	0.57
	Female: 23 (49%)	Female: 31 (43.7%)		
Education level (years)	12.1±4.04	11.08±4.11	73	0.33
Smoking (%)	Yes: 12 (25%)	Yes: 36 (50.7%)	2	**0.02***
Marital status (%)	Married: 15 (31%)	Married: 17 (23.9%)	2	0.53
	Other: 32 (69%)	Other: 54 (76.1%)		
Occupational status (%)	Employed: 36 (76.5%)	Employed: 14 (20%)	1	<**0.001****
	Unemployed: 11 (23.5%)	Unemployed: 57 (80%)		
Age at disease onset (years)	–	29.2±8.2		
The time after the emergence of symptoms (days)		23.7±5.5		
PANSS total score	–	89.8±31.2		
PANSS positive subscale score	–	26.3±10.2		
PANSS negative subscale score	–	23.2±9.4		
PANSS general subscale score	–	43±17.3		

*: P<0.05; **: P<0.001. Chi-Square Test, Fisher's Exact Test, Mann-Whitney U test and Student's t-test were used for statistical analyses. FEP: First episode psychosis; PANSS: The Positive and Negative Syndrome Scale.

brain volumes (17). It has undergone extensive quality checks to ensure accurate and reliable results, validated against manual segmentation methods, and has demonstrated high accuracy in segmenting brain structures. The current study retrieved patient DICOMs (Digital Imaging and Communications in Medicine) from the MRI server. DICOMs were organized into folders, labeled, and modified to fit the processing pipelines. Once the images were prepared, volBrain was used to measure volumes. The total intracranial volume (ICV) was calculated for each subject. Volumes of the basal ganglia, including the putamen, caudate, substantia nigra (SN), globus pallidus (GP), and Nacc, were obtained through automated segmentation and volumetric analysis using volBrain. All MRI images underwent multiple rounds of visual inspection by two separate researchers to ensure accuracy, with manual adjustments made as needed (18, 19).

Statistical Analysis

Data were analyzed using the Statistical Package for the Social Sciences (SPSS) for Windows, version 25.0. The study data were evaluated using various descriptive statistical methods, such as frequency, percentage, mean, and standard deviation. The Kolmogorov-Smirnov test was employed to determine whether the variables conformed to a normal distribution. Categorical variables were compared using the Chi-square test and Fisher's exact test. The Mann-Whitney U test and Student's t-test were used to compare the volumetric data between the independent control and patient groups. The Pearson correlation test was used to examine correlations between basal ganglia volume data and PANSS scores. A logistic regression model was used to determine whether basal ganglia volume could predict the diagnosis of FEP patients. All statistical tests were two-tailed, and significance was determined at the level of $p<0.05$.

RESULTS

Descriptive Data

The study population consisted of 64 males (54.2%) and 54 females (45.8%). The average age of the HC and FEP patients was 31.60±8.2 and 30.90±8.5 years, respectively. There was no significant difference in age (p=0.21), gender ratio (p=0.57), education level (p=0.33), or marital status (p=0.53) between the study groups. The incidence of smoking was higher in the FEP group (p=0.02). The average age of disease onset for FEP patients was 29.2±8.2 years. Detailed clinical data and demographic information are shown in Table 1.

Evaluation of Basal Ganglia Volumes and Correlation with PANSS Scores

A comparison of the basal ganglia volumes (cm^3) between the patients with FEP and the HCs is shown in Figure 2. The volumes of the right (R) and

Table 2: Investigation of the relationship between PANSS scores and basal ganglia volumes

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
1. PANSS total score	1															
2. PANSS positive subscale score	0.62**	1														
3. PANSS negative subscale score	0.77**	0.37**	1													
4. PANSS general subscale score	0.90**	0.40**	0.51**	1												
5. R-caudate	-0.07	0.93	-0.07	-0.11	1											
6. L-caudate	-0.11	-0.01	-0.07	-0.13	0.92**	1										
7. R-putamen	-0.03	0.02	-0.08	-0.02	0.49**	0.50**	1									
8. L-putamen	-0.01	0.05	-0.09	-0.009	0.82**	0.79**	0.51**	1								
9. R-GP	-0.05	-0.08	0.01	-0.06	0.16	0.04	0.40**	0.13	1							
10. L-GP	-0.17	-0.11	-0.01	-0.23	0.27*	0.15	0.08	0.34**	0.41**	1						
11. R-accumbens	-0.03	-0.02	-0.15	0.01	0.44**	0.36**	0.67**	0.39**	0.36**	0.16	1					
12. L-accumbens	-0.01	-0.009	-0.07	0.01	0.33**	0.24*	0.37**	0.38**	0.25**	0.30**	0.47**	1				
13. R-striatum	-0.009	0.006	-0.02	-0.01	0.78**	0.80**	0.77**	0.66**	0.31**	0.08	0.66**	0.29**	1			
14. L-striatum	-0.03	-0.04	-0.03	-0.02	0.86**	0.90**	0.56**	0.88**	0.21*	0.18	0.54**	0.41**	0.83**	1		
15. R-SN	-0.17	0.06	-0.11	-0.23	0.63**	0.62**	0.54**	0.60**	0.22*	0.21*	0.32**	0.38*	0.61**	0.73**	1	
16. L-SN	-0.05	0.05	-0.08	-0.05	0.57**	0.60**	0.46**	0.62**	0.22*	0.25*	0.36**	0.02	0.63**	0.70**	0.63**	1

*: P<0.05; **: P<0.001. Pearson correlation analysis was carried out. GP: Globus pallidus; L: Left; PANSS: The Positive and Negative Syndrome Scale; R: Right; SN: Substantia nigra.

left (L) striatum, R- and L-caudate, and R- and L-SN were found to be higher in FEP patients compared to HCs ($p<0.0001$, $p<0.0001$, $p<0.0001$, $p<0.0001$, $p=0.02$, $p<0.0001$, respectively). While the volume of the L-putamen was higher ($p<0.0001$), the L-GP ($p=0.03$) and L-NAcc ($p=0.04$) were found to be significantly smaller in FEP patients compared to HCs. No significant correlation was found between volume measurements and PANSS scores. Statistical evaluation of the relationship between PANSS scores and basal ganglia volumes is shown in Table 2.

Evaluation of Volumetric Measurements to Predict Diagnosis in Patients with FEP

Volumetric measurements used to predict the diagnosis of SZ are presented in Table 3. A univariate logistic regression model suggested that the volumes of the right (R)-caudate, left (L)-caudate, R-striatum, L-striatum, L-putamen, L-NAcc, R-GP, and L-SN could significantly predict the diagnosis of SZ. The volumes of the R-putamen, R-Nacc, and L-GP did not have any predictive effect on the pathogenesis of SZ.

DISCUSSION

In the current study, basal ganglia volumes were evaluated in drug-naïve patients with FEP and compared to HCs. A remarkable finding of this study is that almost all basal ganglia volumes were higher in patients with FEP compared to the HC group. The basal ganglia, encompassing structures such as the striatum, caudate nucleus, and putamen, play crucial roles in diverse functions, including decision-making, movement, and cognition. These interconnected nuclei interact with the cortex to execute these vital processes. The dorsal corticostriatal circuit governs motor control, while the ventral circuit mediates cognitive and sensory functions (Fig. 1) (6). Importantly, these circuits involve a complex interplay between neurotransmitters like glutamate (excitation) and gamma-aminobutyric acid (GABA, inhibition), with dopamine acting on striatal receptors (6, 20). Dysfunction within these circuits has been implicated in various psychiatric disorders, particularly SZ. While numerous studies have explored potential anomalies using functional imaging techniques such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) (7, 21, 22), this study focuses on structural alterations in SZ using volumetric MRI and PANSS scores for symptom assessment.

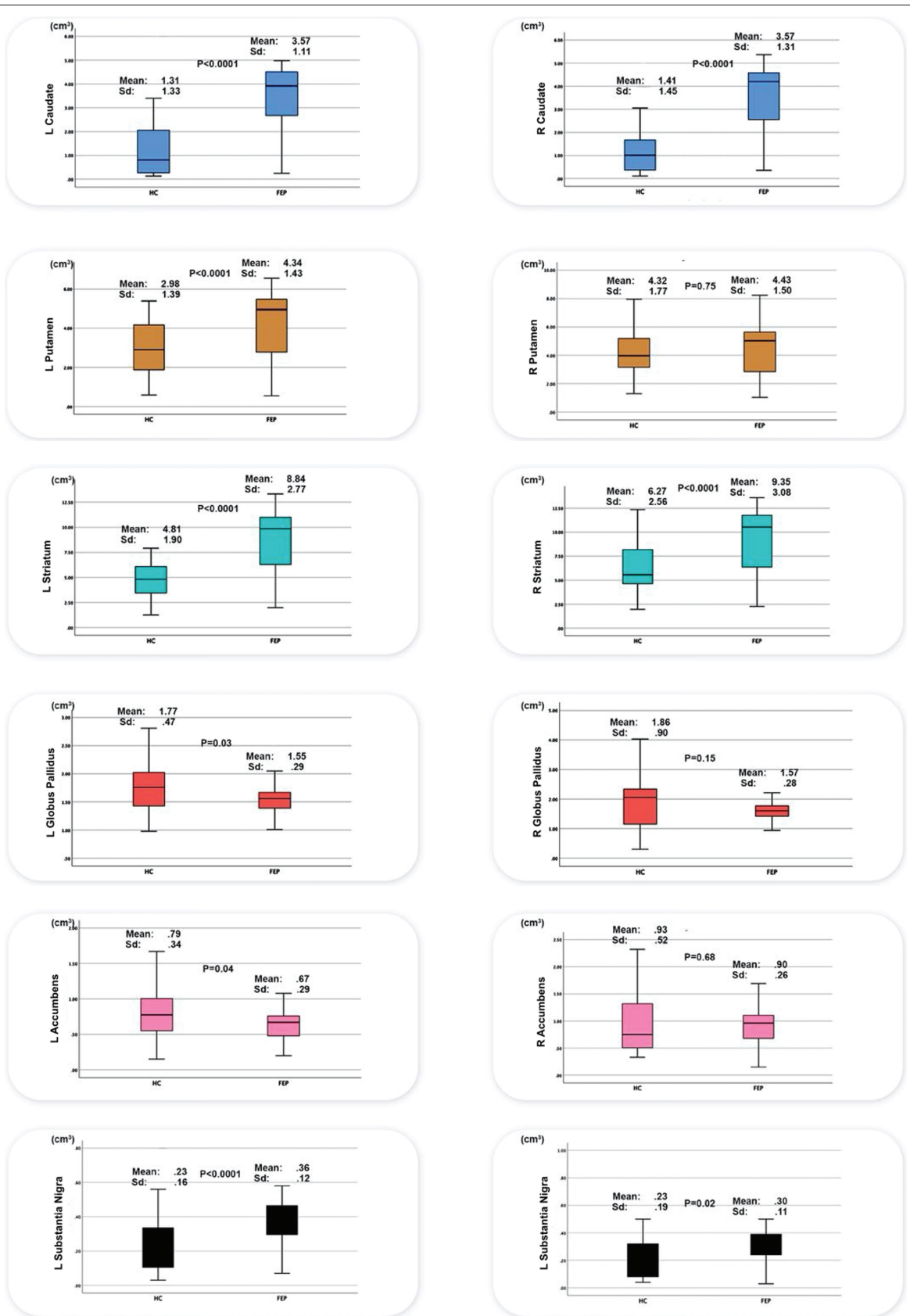

Figure 2. Comparison of the basal ganglia volumes (cm^3) between the patients with FEP and the HC (mean±SD).
L: Left, R: Right, SD: Standard deviation.

Table 3: Univariate Logistic Regression Analysis to identify volumetric variables that can significantly predict FEP in patients

Independent variables	Exp (B)	95.0% CI for β coefficient (Lower-Upper)	Wald	p
R-caudate	2.786	1.80–4.29	21.52	**<0.001****
L-caudate	3.589	2.24–5.74	28.42	**<0.001****
R-striatum	1.41	1.21–1.63	20.04	**<0.001****
L-striatum	1.88	1.41–2.51	18.61	**<0.001****
R-putamen	1.09	0.85–1.41	0.453	0.483
L-putamen	1.87	1.39–2.51	17.5	**<0.001****
R-accumbens	0.815	0.30–2.177	0.166	0.68
L-accumbens	0.136	0.03–0.611	6.78	**0.009***
R-GP	0.42	0.2–0.88	5.25	**0.022***
L-GP	0.167	0.046–0.598	7.55	0.06
R-SN	51.16	1.71–1522.7	5.1	**0.02***
L-SN	557.01	24.1–12835.2	15.6	**<0.001****
Education level	8.7	0.89–85.12	3.61	0.062
Smoking	4.106	1.38–12.13	4.74	**0.033***

*: P<0.05; **: P<0.001. Univariate Logistic Regression Analysis was carried out. FEP: First episode psychosis; GP: Globus pallidus; L: Left; R: Right; SN: Substantia nigra.

Studies investigating dopamine function in individuals at ultra-high risk of psychosis (UHR) have reported that the greatest abnormality was in the associative striatum (23–25). On the other hand, fMRI studies have shown alterations between the cortex and the dorsal striatum in patients with SZ (26–29), and individuals at genetic risk for psychosis (29–31). Meanwhile, studies using diffusion tensor imaging have reported reduced anatomical connectivity between the dorsolateral prefrontal cortex and the associative striatum in patients with SZ (32, 33). Several volumetric studies, which measured the putamen and caudate nucleus separately from the striatum, reported larger striatal volumes in patients with SZ (21, 34). In the current study, we also found increased volumes of both the striatum in the FEP group. There may be several reasons for this. In accordance with the dopamine hypothesis of SZ, elevated dopamine levels in the nigrostriatal pathway may lead to excessive stimulation of striatal D2 receptors, resulting in larger striatum volumes (21). The observed reduction in striatum volume with antipsychotic treatment further supports the relevance of neurotransmitters (35).

The caudate nucleus, involved in the ventral cortical circuit, participates in cognitive functions and the reward pathway. Postmortem studies of patients with SZ have revealed abnormal mitochondrial structures in the glia and neurons of the caudate nucleus (36). Although lower caudate volume was mostly detected in medication-naïve patients in structural MRI studies, research involving larger cohorts has identified larger caudate nuclei in patients with SZ compared to healthy controls (9). A meta-analysis has demonstrated a decrease in the volume of the caudate nucleus in patients, with no volume changes observed in response to treatment (37). In the present study, we found that both caudate nuclei were larger in the FEP group compared to HCs. This discrepancy from other published studies may result from the use of thinner sections in the current study. Additionally, the use of the volBrain program, known for its higher sensitivity in the segmentation of subcortical structures, may have influenced the study results (17). However, an increase in the volume of the caudate nucleus, particularly due to excessive stimulation by the SN and cortex, aligns with the well-established SZ hypothesis.

The putamen, crucial for motor control, has shown inconsistent volumetric changes in SZ. While previous studies reported no significant alterations (11, 37), our findings revealed a larger left putamen in FEP compared to HCs. This suggests potential early-stage neuroanatomical differences, warranting further investigation with multimodal imaging approaches (38). Regarding the GP, traditionally considered hyperactive in SZ with larger volumes reported in some studies (11), our FEP data showed a smaller left GP. This discrepancy could be attributed to several factors. Firstly, previous studies often involved treated patients, while our drug-naïve cohort might

reflect early neurodevelopmental changes. Secondly, the mechanism whereby hippocampal activity drives nucleus accumbens inhibition of the GP to release dopamine (6, 10) suggests that the high striatal volume observed in FEP might suppress the GP via GABAergic mechanisms. Finally, a recent study identified a direct GABAergic projection from the GP to the frontal cortex (39), hinting at potential impairments in ipsilateral connectivity between the basal ganglia and frontal regions in SZ.

In the current study, it can be speculated that the high striatal volume may have led to a decrease in pallidum volume by suppressing the pallidum with excessive GABA secretion (6). The NAcc is the primary structure of the reward pathway and is stimulated by the ventral corticostriatal circuit and the limbic system (20). The NAcc has been associated with negative findings in SZ. Studies have shown a significant decrease in accumbens activity (33), while structural imaging studies have noted a decrease in the volume of the NAcc in SZ (8). In the present study, we also found that the volume of the left NAcc was significantly lower in patients with SZ compared to healthy controls. These data are consistent with findings reported in the literature and support the SZ hypotheses.

Although a non-significant trend toward a negative correlation was observed between PANSS-negative symptoms and the measured intracranial volumes, the association did not reach the threshold for statistical significance. This lack of statistically robust findings could be attributed to several factors, including the inherent heterogeneity of negative symptoms (16). The SN is one of the main sources of dopamine in the brain and forms the nigrostriatal pathway, primarily by interacting with the striatum and D2 receptors (6). Hypofunction of this pathway has been associated with the pathogenesis of Parkinson's disease (40). Moreover, this pathway is a target for antipsychotic drugs and has been implicated in the incidence of extrapyramidal system side effects (10). Although a significant loss of volume in the SN has been detected in Parkinson's disease, there are no clear findings for SZ patients in the literature. To our knowledge, the current study is the first to measure the volume of the SN in SZ. Yoon et al. (27) reported the presence of task-evoked SN hyperactivity; corroborating these findings, we found that SN volumes were significantly higher in FEP patients. This was consistent with functional studies and the pathogenesis of SZ.

While our study provides valuable insights, it is important to acknowledge its limitations. The sample size, though larger than that of some reported studies, might not be sufficient to definitively explain the observed basal ganglia alterations in FEP patients. Additionally, relying solely on subjective symptom history from families could introduce potential bias. Furthermore, the use of volBrain software, while a valid method, differs from some previous studies, potentially contributing to result discrepancies. Implementing additional volumetric analysis methods in future studies could strengthen result validation.

CONCLUSION

The primary finding of this study indicates that the volumes of the striatum, the caudate nucleus, the putamen, and the SN were increased in patients with FEP, whereas a decrease was observed in the volumes of the NAcc and the GP. This suggests that the basal ganglia are impacted from the initial stage of psychosis, including the immediate emergence of symptoms, and may play a role in the pathogenesis of the disorder. However, to ascertain the precise onset of alterations in the basal ganglia, further follow-up studies are needed, which should utilize both functional and structural imaging techniques.

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

Ethical Approval: The Hamidiye Scientific Research Ethics Committee granted approval for this study (date: 13.05.2022, number: 22/275).

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