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RESEARCH ARTICLE

Brain Volume Varies Depending on Symptom Severity and Treatment Response in Schizophrenia

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Abstract
Schizophrenia is a complex psychiatric disorder with varying treatment responses. This study hypothesizes that treatment-resistant schizophrenia patients exhibit distinct structural brain abnormalities compared to treatment-responsive patients and healthy controls. Identifying these differences may provide insight into the neurobiological basis of treatment resistance and guide personalized interventions. A cross-sectional study was conducted with 24 schizophrenia patients and 24 healthy controls. Schizophrenia patients were categorized into treatment responders (≥30% clinical improvement) and treatment-resistant (<30% improvement) based on clinical assessments, including standardized scales and expert evaluation. Among the scales, Positive and Negative Syndrome Scale (PANSS), The Clinical Global Impression Scale (CGI-S), The Global Assessment Scale (GAS), The Brief Psychiatric Rating Scale (BPRS) were used. Brain volumetric data were acquired using MRI and analyzed through the VolBrain platform, focusing on the frontal, temporal, and parietal lobes, cerebellum, and thalamic nuclei. Treatment-resistant demonstrated significantly reduced brain volumes in the frontal, temporal, and parietal lobes, cerebellum, and thalamic nuclei compared to responders and healthy controls ($p<0.05$). Additionally, treatment-resistant had higher scores on the PANSS negative symptom scale and the BPRS, indicating more severe clinical symptoms ($p<0.05$). Responders showed less pronounced volumetric reductions and more favorable clinical profiles. This study reveals that treatment-resistant schizophrenia is associated with marked structural brain abnormalities, particularly in regions critical for cognitive and emotional processing. These findings underscore the potential role of neuroanatomical biomarkers in predicting treatment response and highlight the necessity for targeted therapeutic strategies for treatment-resistant patients.

Keywords
Schizophrenia, PANSS, BPRS, Brain Volume, Treatment

INTRODUCTION

Schizophrenia is a psychiatric disease that is seen in 0.3-0.7 % of the population and has positive symptoms such as delusions and hallucinations; negative symptoms such as shallowness of emotion, social withdrawal, decreased amount of speech, and impoverishment of thought content; cognitive symptoms such as impairment in attention, memory, executive functions; and affects emotions, thoughts, perception, behavior; and also sometimes can present with different clinical pictures (McCutcheon et al., 2020; Tandon et al., 2024). Schizophrenia is a chronic, multifaceted disorder that typically begins at a young age and significantly disrupts interpersonal and occupational functioning, leading to a decline in abilities. It often causes individuals to diverge from conventional perceptions and interpretations, resulting in societal withdrawal and conflicts with their environment. The convergence of these symptoms characterizes schizophrenia as a condition with both neurodevelopmental and neurodegenerative aspects, which might be leading to structural abnormalities (Tandon et al., 2024). Numerous studies have utilized brain volumetric measurements to track neurodevelopmental processes in schizophrenia (Deniz et al., 2024; Sen

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et al., 2023). In our previous research, we also conducted detailed measurements of brain volumes in patients with schizophrenia (Deniz et al., 2024). Brain volume measurements are crucial in schizophrenia as they offer valuable insights into the structural abnormalities associated with the disorder. Research indicates that individuals with schizophrenia often exhibit reductions in gray matter, accompanied by increases in cerebrospinal fluid and ventricular volumes (Deniz et al., 2024; Yamazaki et al., 2024). These volumetric changes are instrumental in understanding the neuroanatomical underpinnings of the disorder and tracking its progression. Although brain volume measurements have been extensively evaluated in patients with schizophrenia, studies focusing on structural brain changes associated with positive and negative symptoms, as well as changes in brain volume ratios after treatment, remain limited. Our study aims to investigate structural brain changes in individuals diagnosed with schizophrenia by grouping them according to clinical evaluation, PANSS, CGI-S, GAS, and BPRS measurements, and their response to treatment, and then comparing them with healthy controls. This approach seeks to obtain detailed data on the neurobiology of the disorder.

MATERIALS AND METHODS

Study Description and Ethics Approval

This study is a retrospective cross-sectional study. The minimum number of patients required for the present study was determined by the prior sample size calculation section of the G*Power 3.1.9.7 program (Software, concept, and design of the University of Kiel, Germany, free Windows software by Franz). The study determined that with an effect size of 0.5, a power of 0.95 could be achieved within a 95% confidence interval, with a significance level set at 0.05. These parameters were chosen to ensure robust statistical power and confidence in the results (Cheng et al., 2022).

This research complied with the principles of the Helsinki Declaration and with ethical approval from the Atatürk University Medical Ethics Committee meeting numbered B.30.2.ATA.0.01.00/805, dated October 26, 2023. Participant provided informed consent, with the volunteer form covering research details, risks, benefits, confidentiality, and participant rights. The research strictly adhered to the ethical principles of the Declaration of Helsinki, prioritizing participant's rights and well-being in design, procedures, and confidentiality measures.

This study is a retrospective analysis of medical records/archived samples. Before accessing the data, all documents were fully anonymized to ensure confidentiality and compliance with ethical standards. Additionally, the Institutional Review Board (IRB)/ethics committee waived the requirement for informed consent, as the study involved only de-identified retrospective data.

Study Design

This study employed a cross-sectional design to investigate structural brain changes in individuals diagnosed with schizophrenia. Participants' data on the MRI age, PANSS, CGI-S, GAS, and BPRS were evaluated from their medical records. Additionally, individuals diagnosed with schizophrenia were divided into two subgroups: treatment responders (those who showed more than a 30% improvement from treatment) treatment-resistant and (those who showed 30% or less improvement from treatment). These groups were then compared with a control group of healthy individuals. Detailed examinations were conducted on all participants' frontal, temporal, and parietal lobes, cerebellum, and thalamic nuclei.

In this study, treatment response was defined as a ≥30% reduction in PANSS total score from baseline to the time of MRI evaluation. This criterion aligns with standard definitions in schizophrenia research, where a decrease of 30% in PANSS total score is generally considered indicative of clinically meaningful improvement in symptom severity (Ogyu et al., 2020).

The percentage change was calculated using the formula: % improvement-(Baseline PANSS total score-Follow-up PANSS total score/Baseline PANSS total score)×100

Participants achieving a reduction of ≥30% were categorized as treatment responders, while those achieving <30% were classified as treatment-resistant.

This classification was confirmed by a senior psychiatrist (co-author HÖ) through an integrative clinical assessment including PANSS scores, CGI-S ratings, BPRS scores, patient and caregiver interviews, medical records, and functional assessments, following clinical practice standards for comprehensive evaluation.

Participants

This study utilized clinical data from 24 patients diagnosed with schizophrenia according to the criteria specified in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5). These patients, who had no other neurological disorders, were followed up in the Department of Psychiatry at the University Hospital between 2021 and 2024. The most recent psychiatric scores of schizophrenia patients on their MRI dates were taken as a basis. The control group consisted of 24 individuals without neurological diseases, selected from the University Hospital archive records and matched with the patient group regarding sociodemographic characteristics. The cohort included 20 males and four females, reflecting the higher prevalence of schizophrenia among males in the experimental group as mentioned in the literature. Similarly, the control group comprised twenty males and four females, ensuring consistency with the experimental group. Patient groups were not only grouped according to the clinical improvement and scale scores. But also evaluated and grouped by a senior psychiatrist who is one of the researcher on this paper working as professor of psychiatry in the hospital data were taken from, also following half of the patients in the study by himself, and also evaluating all of the patients data including not only scales, the anamnesis from the patient and relatives, epicriris, life functionality, etc; meticulously.

Assessment Tools

PANSS: The assessment tool developed by Kay et al (Kay et al., 1987) is designed to evaluate general psychopathology and measure the severity of these symptoms. It is administered through a semi-structured interview lasting 30-40 minutes, pagathered from the patient's relatives and the healthcare personnel responsible for the patient's care. The tool comprises 30 items: seven positive, seven negative, and 16 general psychopathology symptoms. Each item's severity is rated on a scale from 1 to 7, and the scores are summed to obtain the final score (Kirpinar & Demirel, 2024).

CGI-S: The Clinical Global Impression Scale, developed by Guy et al (Guy, 1976), is a brief assessment tool used to evaluate the course of psychiatric disorders across all age groups. The scale has three dimensions: severity of illness, global improvement, and side effect levels. The first dimension assesses the severity of the disease on a scale from 1 to 7, the second dimension evaluates improvement from 1 to 7, and the third dimension measures the severity of medication side effects on a scale from 1 to 4. The severity of illness scale includes the following items: 1 = normal, not ill; 2 = borderline ill; 3 = mildly ill; 4 = moderately ill; 5 = significantly ill; 6 = severely ill; 7 = very severely ill. This study utilized the dimension indicating the severity of the disease.

GAS: The Global Assessment Scale, developed by Endicott (Endicott et al., 1976), is a rating scale that can be administered quickly and encompasses all aspects of changes in psychopathology, including psychological, social, and occupational functioning. It is scored on a scale from 0 to 100.

BPRS: The Brief Psychiatric Rating Scale is a widely used tool that lets clinicians quickly assess the presence and severity of various psychiatric symptoms. In this study, the 18-item version of the scale was utilized. Each item is scored on a scale from 0 to 6, reflecting the severity of the symptom. The total score ranges from 0 to 108, with higher scores indicating greater symptom severity (Arathil et al., 2024).

Brain Imaging MRI Protocol

This study's MRI (3 Tesla, Siemens Magnetom Prisma) protocol included high-resolution T1-weighted 3D Magnetization Prepared Rapid Gradient Echo (MPRAGE) sequences for anatomical visualization. The data were acquired retrospectively during routine clinical procedures. Imaging parameters were as follows: sagittal orientation; repetition time (TR) of 1900 ms; echo time (TE) of 2.67 ms; flip angle of 15°; field of view (FOV) of 256 × 256 mm^2; matrix size of 256 × 256; 160 slices with a thickness of 1 mm each; and isotropic spatial resolution of 1 × 1 × 1 mm^3. (Deniz et al., 2023, 2024).

Image Processing and Analysis

VolBrain Method

The study employed VolBrain (https://volbrain.net/), an open-access platform for automated segmentation of diverse brain structures. Utilizing default VolBrain T1-weighted volumetric images, total cerebrum volumetric analysis was conducted across the study groups. Additionally, the study used the Mricloud method, a web-based software developed by Johns Hopkins University, for volume calculation, incorporating brain parcellation in MR images. To facilitate volume calculation using VolBrain, MR images underwent conversion to either 'gz' or 'rar' format. The process

involved a series of prescribed steps to enable accurate volumetric analyses. The process commences with opening a file denoted by the extension 'DICOMDIR' via a DICOM viewer software application. Subsequently, to visualize the anatomical structure, high-resolution T1-weighted 3D Magnetization Prepared Rapid Gradient Echo (MPRAGE) images are accessed using the software 'mricron', culminating in the creation of a compressed file with a 'gz' extension in the FSL format. Following this initial step, the images, now converted to 'gz' format, are uploaded onto the VolBrain web interface. Registration procedures are executed, whereby the 'gz' extension files are submitted to the system for processing. Upon upload completion, the system initiates volumetric analyses for all brain regions. The volumetric data obtained is then saved to the registered e-mail address in Portable Document Format (PDF) and Comma Separated Values (CSV) (Deniz et al., 2024).

In this study, the AssemblyNet partition was selected from VolBrain measurements. AssemblyNet is a large CNN ensemble for 3D whole-brain MRI segmentation. Volumetric values of all parts of the brain were measured in cm3 and percentages, and total-right-left ratios were measured. A total of 512 different data points were obtained from each participant. White Matter (WM), Grey Matter (GM), Subcortical GM, Cortical GM, Cerebellar GM, Cerebro Spinal Fluid (CSF), Brain (WM+GM), Intracranial Cavity (IC), Cerebellum Total, Cerebellum WM, Cerebellum GM, and Vermis, Among the cortical structures, Frontal lobe and Frontal lobe parts, the Frontal pole, Gyrus rectus, Opercular inferior frontal gyrus, Orbital inferior frontal gyrus, Triangular inferior frontal gyrus, Medial frontal cortex, Middle frontal gyrus, Anterior orbital gyrus, Lateral orbital gyrus, Medial orbital gyrus, Posterior orbital gyrus, Precentral gyrus, Precentral gyrus medial segment, Subcallosal area, Superior frontal gyrus, Superior frontal gyrus medial segment, supplementary motor cortex were measured. The temporal lobe and Fusiform gyrus, Planum polare, Planum temporale, Inferior temporal gyrus, Middle temporal gyrus, Superior temporal gyrus, Transverse temporal gyrus, and Temporal pole were measured. The parietal lobe and Angular gyrus, Postcentral gyrus, Postcentral gyrus medial segment, Precuneus, Superior parietal lobule, and Supramarginal gyrus were measured (Deniz et al., 2024). Thalamus nuclei were measured in the “Deepthalamus” part in the base nuclei part (Figure 1).

Statistical Analysis

All statistical analyses were performed using IBM Corporation's Statistical Package for the Social Sciences (SPSS) version 22.0. Data were presented as means and standard deviations. Kurtosis and skewness values indicated the data did not follow a normal distribution (between −2 and +2). As nonparametric test assumptions were met, nonparametric data from two groups were analyzed using the Mann-Whitney U test. In comparison, data from three groups were analyzed using the Kruskal-Wallis test. The significance level for all comparisons was set at $p<0.05$.

RESULTS

This study included three groups. Group 1 consisted of individuals with schizophrenia who responded to treatment, defined as those showing more than a 30% clinical improvement according to the scales. This group included 15 participants (13 males, 2 females) with an average age of 34.07±6.21 years. Group 2 comprised individuals with schizophrenia who did not respond to treatment, defined as those showing 30% or less improvement. This group included 9 participants (7 males, 2 females) with an average age of 38.00±15.01 years. Group 3 was the control group, consisting of 24 healthy individuals (20 males, 4 females) without neurological conditions.

Their average age was 34.24±4.98 years. There is no statistically significant difference between the age groups ($p<0.05$). The scores of individuals diagnosed with schizophrenia on the PANSS, CGI-S, GAS, and BPRS measurements were grouped according to their treatment response and are presented in Table 1.

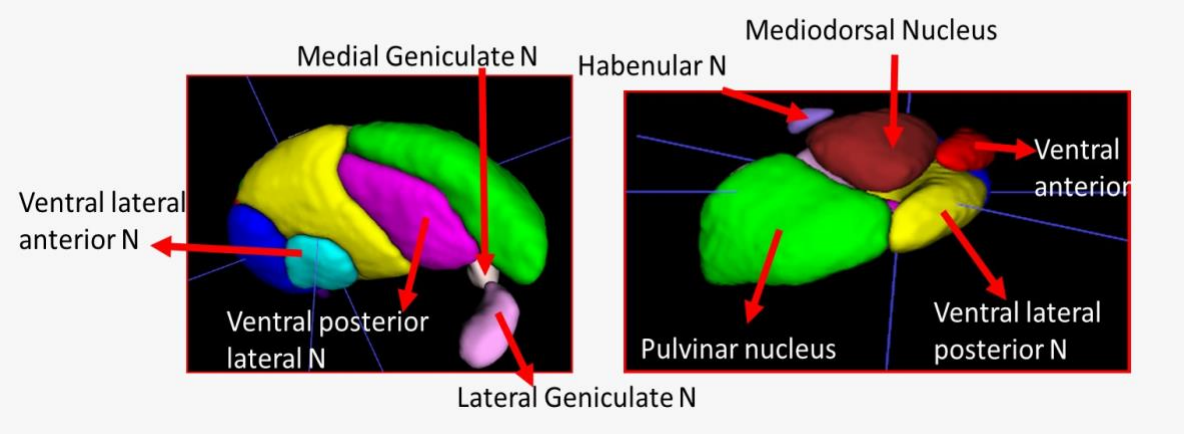

Figure 1. Thalamic Nuclei Anatomical Segmentation and Labeling

Table 1. PANSS. CGI-S. GAS and BPRS measurements and descriptive ınformation in schizophrenia patients

	Schizophrenia Group	X±SD	P
Age	**Responsive to Treatment**	34.07±6.21	0.376
	Treatment-resistant	38±15.01	
MRI Age	**Responsive to Treatment**	29.53±5.64	0.228
	Treatment-resistant	35.57±17.34	
PANSS positive total score	**Responsive to Treatment**	26.±5.52	0.972
	Treatment-resistant	25.88±10.53	
PANSS negative total score	**Responsive to Treatment**	22.23±8.53	0.014*
	Treatment-resistant	32.00±7.01	
PANSS general psychopathology total score	**Responsive to Treatment**	43.69±11.56	0.103
	Treatment-resistant	52.50±11.27	
PANSS total score	**Responsive to Treatment**	91.93±20.73	0.78
	Treatment-resistant	110.50±25.65	
CGI-S	**Responsive to Treatment**	5±0.81	0.178
	Treatment-resistant	5.50±0.75	
GAS	**Responsive to Treatment**	37.85±11.52	0.148
	Treatment-resistant	30.43±7.97	
BPRS	**Responsive to Treatment**	33.50±15.05	0.044*
	Treatment-resistant	52.80±20.01	
RECOVERY	**Responsive to Treatment**	0.57±0.12	0.001**
	Treatment-resistant	0.23±0.07	

PANSS: Positive and Negative Syndrome Scale, CGI-S: Clinical Global Impressions Scale, GAS: Global Assessment Scale, BPRS: Brief Psychiatric Rating Scale, MRI: Magnetic Resonance Imaging, X±SD: Mean ± Standard Deviation

In the study, detailed brain volume measurements were calculated for both schizophrenia patients and healthy controls. Statistically significant differences were observed in WM, GM, Cortical GM, Total Brain GM and WM, Cerebellar GM, IC, total cerebrum, left cerebrum, total cerebrum WM, left cerebrum WM, and total cerebrum GM volume measurements between schizophrenia patients who did not respond to treatment, those who did respond, and healthy controls ($p<0.05$). Detailed measurement data were provided in Table 2.

Table 2. Comparison of the volume and percentage ratios of white matter and grey matter in the cerebrum and cerebellum between individuals with schizophrenia and the control group

	RTT X±SD	TRE X±SD	Control X±SD	RTT-TRE	RTT-Control	TRE-Control	RTT-TRE-Control
Grey Matter cm^3	797.87±46.61	664.18±104.78	799.76±79.91	0.005*	0.495	0.001**	0,001**
Grey Matter %	51.99±6.77	50.95±4.64	55.63±2.55	0.051	0.999	0.037*	0,005**
White Matter cm^3	513.23±126.41	381.14±44.96	468.67±39.05	0.014*	0.899	0.013*	0,004**
White Matter %	32.57±2.23	29.42±3.01	32.65±1.87	0.961	0.178	0.051	0,022*
Subcortical cm^3	38.12±18.80	35.36±10.01	43.59±5.17	0.955	0.639	0.120	0,061
Subcortical %	2.60±1.30	2.73±0.76	3.03±0.30	0.985	0.541	0.636	0,452
Cortical GM cm^3	636.66±41.30	526.01±89.27	641.84±71.05	0.017*	0.989	0.013*	0,004**
Cortical GM %	41.43±5.08	40.28±3.78	44.62±2.52	0.901	0.104	0.027*	0,008**
Cerebellar GM cm^3	123.08±13.73	102.80±12.08	114.32±10.35	0.004*	0.127	0.074	0,003**
Cerebellar GM %	7.96±0.91	7.93±0.76	7.97±0.61	0.999	0.999	0.999	0,882
CSF cm^3	239.90±173.27	243.30±95.83	151.11±54.79	0.999	0.202	0.063	0,044*
CSF %	14.29±6.54	18.46±6.32	10.47±3.60	0.366	0.147	0.015	0,006**
Brain (WM+GM) cm^3	1311.10±143.28	1045.33±141.43	1268.44±113.29	0.001**	0.709	0.003**	0,001**
Brain (WM+GM) %	84.57±6.26	80.38±6.21	88.29±3.60	0.338	0.142	0.014*	0,004**
Intracranial Cavity cm^3	1567.79±297.71	1303.49±166.32	1437.19±120.61	0.032*	0.328	0.140	0,010*
Cerebrum total cm^3	1163.95±136.43	919.97±130.13	1130.10±106.62	0.001**	0.806	0.003**	1,000
Cerebrum total %	75.01±5.21	70.71±5.78	78.64±3.58	0.240	0.078	0.009**	0,001**
Cerebrum right cm^3	588.11±96.64	493.52±102.13	561.03±54.86	0.113	0.705	0.245	0,003**
Cerebrum right %	37.73±2.58	37.81±5.48	39.05±2.23	0.999	0.305	0.895	0,074
Cerebrum left cm^3	575.83±48.15	426.45±95.30	569.07±54.19	0.004**	0.969	0.005**	0,279
Cerebrum left %	37.27±3.35	32.89±6.58	39.59±1.58	0.251	0.065	0.047*	0,001**
Cerebrum total WM cm^3	489.16±130.05	358.60±43.01	444.66±38.05	0.006**	0.517	0.001**	0,001**
Cerebrum total WM %	30.96±2.33	27.68±2.95	30.98±1.81	0.039*	0.999	0.031*	0,004**
Cerebrum right WM cm^3	259.59±91.38	194.56±45.50	221.17±19.40	0.088	0.340	0.0326	0,024*
Cerebrum right WM %	16.24±2.14	14.97±3.09	15.41±1.05	0.659	0.453	0.970	0,300
Cerebrum left WM cm^3	229.57±47.15	164.03±39.79	223.48±19.48	0.005**	0.954	0.005**	0,001**
Cerebrum left WM %	14.72±1.82	12.71±3.14	15.56±0.83	0.287	0296	0.077	0,001**
Cerebrum total GM cm^3	674.78±44.57	561.37±94.67	685.43±74.16	0.021*	0.925	0.012*	0,006**
Cerebrum total GM %	44.03±6.19	43.02±4.22	47.66±2.58	0.953	0.132	0.033*	0,017*
Cerebrum right GM cm^3	328.52±46.83	298.95±62.08	339.85±38.54	0.558	0.824	0.255	0,301
Cerebrum right GM %	21.49±4.23	22.83±2.84	23.63±1.57	0.740	0.214	0.827	0,457
Cerebrum left GM cm^3	346.25±35.46	262.41±63.52	345.58±37.26	0.012	0.999	0.012	0,003**
Cerebrum left GM %	22.54±3.03	20.18±4.14	24.02±1.17	0.409	0.246	0.071	0,003**
Cerebellum total cm^3	128,81±11,50	113,10±11,87	132,33±14,19	0.017*	0.786	0.003**	0,004**
Cerebellum total %	8,75±0,88	8,79±0,92	8,93±0,97	0.999	0.916	0.976	0,771
Cerebellum right cm^3	63,68±6,66	59,78±8,43	67,22±6,79	0.590	0.317	0.102	0,073
Cerebellum right %	4,34±0,60	4,62±0,41	4,54±0,48	0.491	0,666	0,952	0,470
Cerebellum left cm^3	65,13±8,13	53,31±8,42	65,10±7,63	0.011*	0.999	0.008**	0,003**
Cerebellum left %	4,41±0,42	4,17±0,77	4,39±0,50	0.803	0.999	0.830	0,892
Cerebellum WM total cm^3	23,67±6,65	21,29±3,76	24,72±4,25	0.619	0.931	0.112	0,082
Cerebellum WM total %	1,63±0,48	1,65±0,28	1,69±0,36	0.998	0.961	0.986	0,883
Cerebellum WM right cm^3	12,24±2,61	12,10±3,07	12,88±1,78	0.999	0.793	0.865	0,711
Cerebellum WM right %	0,84±0,19	0,93±0,20	0,87±0,14	0.636	0.922	0.824	0,707
Cerebellum WM left cm^3	11,43±4,08	9,18±3,90	11,83±3,17	0.483	0.984	0.253	0,041*
Cerebellum WM left %	0,78±0,28	0,72±0,31	0,81±0,22	0.941	0981	0.806	0,887
Cerebellum GM total cm^3	105,13±10,69	91,81±9,86	107,60±13,66	0.018*	0.899	0.005**	0,005**
Cerebellum GM total %	7,12±0,58	7,14±0,75	7,24±0,67	0.989	0.926	0.981	0,676
Cerebellum GM right cm^3	51,43±4,75	47,68±5,90	54,33±5,63	0.336	0.258	0.034	0,016*
Cerebellum GM right %	3,50±0,43	3,68±0,24	3,66±0,35	0.503	0.571	0.996	0,335
Cerebellum GM left cm^3	53,70±9,63	44,12±7,29	53,27±8,40	0.036*	0.999	0.021*	0,007**
Cerebellum GM left %	3,62±0,41	3,45±0,63	3,57±0,34	0.867	0.979	0.933	0,938
Vermis cm^3	11,64±1,91	9,15±3,49	11,35±2,07	0.210	0.961	0.286	0.020*
Vermis %	0,79±0,12	0,70±0,25	0,78±0,16	0.755	0.996	0.815	0.672

RTT: Responsive to Treatment, TRE: Treatment-resistant, X±SD: Mean ± Standard Deviation, CSF: Cerebro Spinal Fluid, WM: White Matter, GM: Grey Matter. **: $p<0.01$. *: $p<0.05$

In measurements of the frontal lobe, the volumes of the inferior frontal gyrus, triangular inferior frontal gyrus, and middle frontal gyrus were found to be significantly lower in schizophrenia patients who did not respond to treatment compared to those who did respond (Table 3).

Table 3. Comparison of the detailed volume and percentage ratios of frontal lobe, temporal lobe, parietal lobe between individuals with schizophrenia and the control group

	RTT X±SD	TRE X±SD	Control X±SD	RTT-TRE	RTT-Control	TRE-Control
Frontal lobe	205.52±15.39	170.42±28.20	205.15±23.29	0.017*	0.999	0.018*
Frontal pole	7.70±2.01	6.80±1.22	7.59±1.10	0.464	0.996	0.307
Gyrus rectus	4.01±1.74	3.51±1.13	4.75±1.06	0.795	0.387	0.040*
Opercular inf. frontal gyrus	6.93±2.06	6.16±1.01	7.41±0.94	0.552	0.803	0.020*
Orbital inf. frontal gyrus	3.24±1.12	2.75±0.86	3.32±0.82	0.569	0.994	0.298
Triangular inf. frontal gyrus	8.19±1.36	6.74±1.16	8.06±1.71	0.035*	0.989	0.058
Medial frontal cortex	3.44±1.65	2.97±1.30	3.99±1.18	0.837	0.619	0.177
Middle frontal gyrus	50.32±15.61	36.77±6.99	44.94±6.09	0.025*	0.524	0.026*
Anterior orbital gyrus	4.68±1.23	4.05±0.84	5.06±1.04	0.386	0.703	0.030*
Lateral orbital gyrus	5.52±1.08	4.31±1.44	5.62±0.95	0.142	0.988	0.087
Medial orbital gyrus	8.36±3.04	8.27±1.90	9.96±1.30	0.998	0.195	0.093
Posterior orbital gyrus	7.14±2.03	5.76±1.60	7.04±1.27	0.224	0.998	0.151
Precentral gyrus	28.10±4.41	23.86±4.35	29.63±2.68	0.100	0.557	0.011*
Precentral gyrus medial seg.	5.45±1.26	4.79±1.25	5.75±0.74	0.552	0.793	0.159
Subcallosal area	2.17±0.90	2.26±0.81	2.87±0.85	0.994	0.068	0.210
Sup. frontal gyrus	34.70±4.49	28.66±6.20	32.90±5.09	0.071	0.590	0.249
Sup. frontal gyrus medial seg.	13.63±2.36	12.42±3.49	14.54±2.71	0.757	0.621	0.334
Supplementary motor cortex	11.86±2.35	10.25±1.96	11.65±1.33	0.235	0.984	0.205
Temporal lobe	129.71±11.30	104.47±22.81	134.95±16.37	0.032*	0.571	0.011*
Fusiform gyrus	18.73±2.65	13.90±4.25	18.67±2.71	0.029*	0.997	0.030*
Planum polare	3.48±1.44	3.18±0.92438	4.55±0.70	0.904	0.044*	0.005**
Planum temporale	3.7443±1.90	2.67±1.07	4.08±1.17	0.256	0.900	0.015
Inf. temporal gyrus	31.03±8.12	25.91±4.18	29.79±4.17	0.155	0.932	0.093
Middle temporal gyrus	33.11±3.92	27.34±6.65	35.38±3.96	0.106	0.249	0.019
Sup. temporal gyrus	15.81±1.65	12.46±2.53	17.46±2.17	0.012*	0.034*	0.001**
Transverse temporal gyrus	3.05±1.18	2.28±0.66	3.20±0.55	0.150	0.955	0.008**
Temporal pole	20.71±2.31	16.69±5.32	21.77±3.84	0.164	0.643	0.069
Parietal lobe	131.56±13.28	109.75±19.27	128.93±15.52	0.032*	0.925	0.059
Angular gyrus	29.35±11.28	23.97±9.97	27.42±4.12	0.558	0.897	0.714
Postcentral gyrus	23.07±3.68	20.90±2.62	26.14±2.91	0.288	0.034*	0.001**
Postcentral gyrus medial seg.	2.28±1.09	1.97±0.49	2.32±0.42	0.725	0.999	0.221
Precuneus	25.85±3.26	21.19±4.95616	26.50±4.66	0.078	0.941	0.044*
Sup. parietal lobule	30.51±8.37	24.17±4.36	25.89±3.85	0.069	0.169	0.682

RTT: Responsive to Treatment, TRE: Treatment-resistant, X±SD: Mean ± Standard Deviation, Sup: Superior. Inf: Inferior, Seg:Segment. **: p<0.01. *: p<0.05

In measurements of the parietal lobe, the volumes of the postcentral gyrus and precuneus were found to be significantly lower in schizophrenia patients who did not respond to treatment compared to healthy controls. In measurements of the parietal lobe, the volumes of the total parietal lobe were found to be significantly lower in schizophrenia patients who did not respond to treatment compared to those who did respond (Table 3). In the measurement of the thalamus, the volumes of the total thalamus, left thalamus, Anterior Ventral Nuclei (AVN) total, right AVN, right Ventral Anterior Nuclei (VAN), left VAN, Ventral Lateral Posterior Nuclei (VLPN) total, right VLPN, Pulvinar Nuclei (PN) total, right PN, left PN, Lateral Geniculate Nuclei (LGN) total, right LGN, left LGN, Medial Geniculate Nuclei (MGN) total, right MGN, left MGN, right Centromedian Nuclei (CN), Mediodorsal Nuclei (MN) total, proper MN, left MN, Habenular Nuclei (HN) total, right HN, and left HN were all found to be significantly lower in schizophrenia patients who did not respond to treatment compared to those who did respond (Figure 2). All detailed data were shown in Tables 2-4.

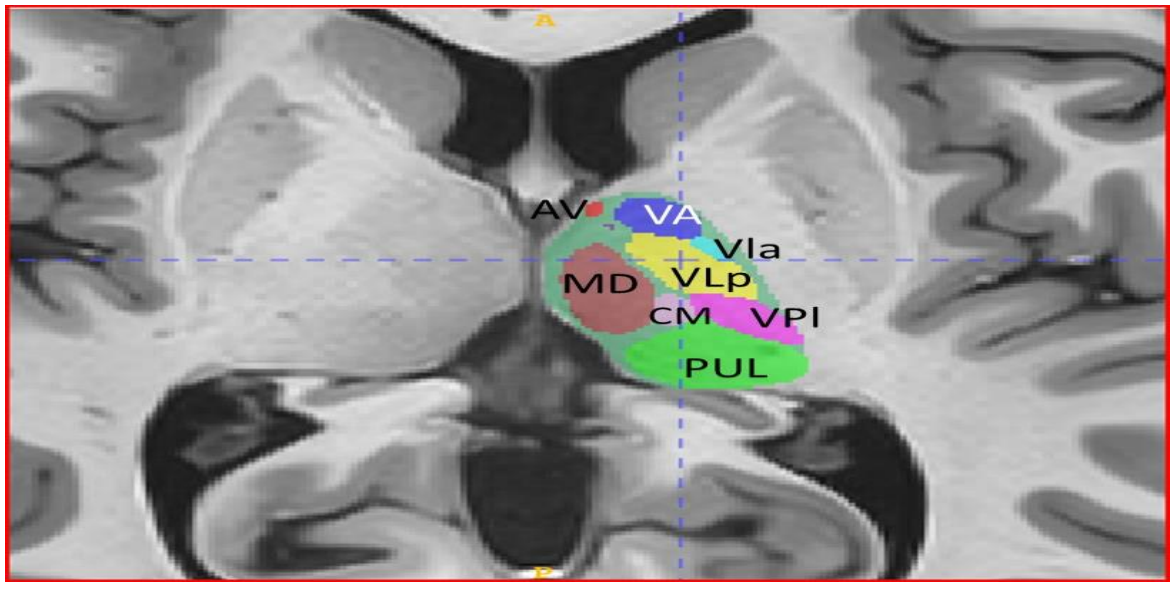

Figure 2. Thalamic nuclei segmentation on Axial MRI.

Table 4. Comparison of the volume and percentage ratios of thalamus between ındividuals with schizophrenia and the control groups

	RTT X±SD	TRE X±SD	Control X±SD	RTT-TRE	RTT-Control	TRE-Control	RTT-TRE-Control
Thalamus total volume	11.05±3.41	5.13±5.50	12.02±1.70	0.039*	0.688	0.016*	0.002**
Thalamus total volume %	10.34±36.76	79.93±75.07	0.86±.113	0.075	0.706	0.040*	0.292
Thalamus right volume	5.46±1.77	2.61±2.83	6.11±0.67	0.056	0.472	0.018*	0.001**
Thalamus right volume %	4.36±15.29	33.32±31.22	0.43±0.04	0.075	0.708	0.040*	0.204
Thalamus left volume	5.58±1.65	2.52±2.68	5.90±1.07	0.028*	0.888	0.015*	0.002**
Thalamus left volume %	5.97±21.47	46.61±43.85	0.42±0.07	0.076	0.704	0.040*	0.292
Thalamus volume asym.	-5.15±11.48	-15.35±23.34	5.18±15.87	0.574	0.071	0.096	0.008**
AVN total volume	0.18±0.06	0.07±0.09	0.17±0.06	0.039*	0.999	0.038*	0.008**
AVN total volume %	0.05±0.15	0.34±0.31	0.01±0.01	0.076	0.684	0.039*	0.044*
AVN right volume	0.091±0.03	0.03±0.04	0.08±0.03	0.017*	0.893	0.037*	0.005**
AVN right volume %	0.02±0.06	0.14±0.13	0.01±0.01	0.078	0.663	0.040*	0.043*
AVN left volume	0.08±0.03	0.04±0.04	0.09±0.02	0.086	0.965	0.044*	0.012*
AVN left volume %	0.02±0.08	0.19±0.17	0.01±0.01	0.075	0.701	0.039*	0.037*
VAN total volume	0.53±0.16	0.22±0.26	0.59±0.11	0.075	0.701	0.039*	0.002**
VAN total volume %	0.18±0.54	1.21±1.12	0.04±0.01	0.077	0.709	0.040*	0.383
VAN right volume	0.26±0.07	0.10±0.12	0.27±0.06	0.021*	0.846	0.010*	0.003**
VAN right volume %	0.07±0.19	0.44±0.40	0.01±0.01	0.078	0.700	0.041*	0.265
VAN left volume	0.27±0.09	0.11±0.13	0.31±0.06	0.026*	0.419	0.006**	0.001**
VAN left volume %	0.11±0.34	0.77±0.71	0.02±0.01	0.076	0.714	0.040*	0.372
VLAN total volume	0.17±0.05	0.08±0.09	0.19±0.04	0.083	0.496	0.024*	0.010*
VLAN total volume %	0.02±0.03	0.09±0.07	0.01±0.01	0.074	0.752	0.041*	0.063
VLAN right volume	0.08±0.02	0.03±0.04	0.09±0.02	0.068	0.586	0.022*	0.006**
VLAN right volume %	0.01±0.01	0.04±0.03	0.01±0.01	0.076	0.735	0.041*	0.070
VLAN left volume	0.08±0.03	0.04±0.05	0.09±0.02	0.108	0.478	0.028*	0.013*
VLAN left volume %	0.01±.01	0.04±0.03	0.01±0.01	0.072	0.769	0.040*	0.058
VLPN total volume	1.52±0.50	0.66±0.76	1.69±0.25	0.034*	0.535	0.011*	0.001**
VLPN total volume %	0.44±1.25	2.81±2.56	0.12±0.01	0.076	0.714	0.040*	0.320
VLPN right volume	0.76±0.24	0.31±0.37	0.82±0.17	0.020*	0.802	0.009**	0.001**
VLPN right volume %	0.16±0.40	0.91±0.82	0.05±0.01	0.079	0.704	0.041*	0.373
VLPN left volume	0.75±0.26	0.35±0.40	0.86±0.10	0.059	0.329	0.014*	0.001**
VLPN left volume %	0.27±0.85	1.90±1.74	0.06±0.01	0.075	0.718	0.040*	0.151
VPLN total volume	0.62±0.21	0.32±0.39	0.66±0.12	0.178	0.827	0.092	0.095
VPLN total volume %	0.09±0.17	0.41±0.34	0.04±0.01	0.069	0.708	0.036*	0.001**
VPLN right volume	0.30±0.10	0.15±0.19	0.32±0.08	0.144	0.972	0.096	0.069
VPLN right volume %	0.04±0.08	0.20±0.16	0.02±0.01	0.071	0.684	0.036*	0.003**
VPLN left volume	0.31±0.10	0.17±0.20	0.34±0.05	0.222	0.604	0.091	0.230
VPLN left volume %	0.04±0.08	0.21±0.17	0.02±0.01	0.068	0.731	0.036*	0.001**
PN total volume	2.47±0.77	1.06±1.19	2.67±0.48	0.024*	0.785	0.011*	0.001**
PN total volume %	1.42±4.78	10.47±9.77	0.19±0.03	0.076	0.705	0.040*	0.371
PN right volume	1.25±0.39	0.50±0.60	1.31±0.27	0.018*	0.919	0.010*	0.001**
PN right volume %	0.30±0.80	1.82±1.65	0.09±0.02	0.078	0.698	0.041*	0.375
PN left volume	1.22±0.38	0.55±0.59	1.35±0.21	0.033*	0.607	0.012*	0.001**
PN left volume %	1.12±3.97	8.65±8.12	0.09±0.01	0.076	0.706	0.040*	0.314
LGN total volume	0.13±0.05	0.04±0.05	0.12±0.05	0.008**	0.971	0.011*	0.005**

Table 4. Continue

	RTT X±SD	TRE X±SD	Control X±SD	RTT-TRE	RTT-Control	TRE-Control	RTT-TRE-Control
LGN total volume %	0.05±0.16	0.36±0.34	0.01±0.01	0.078	0.689	0.040*	0.151
LGN right volume	0.06±0.02	0.02±0.02	0.06±0.02	0.011*	0.991	0.012*	0.006**
LGN right volume %	0.03±0.12	0.27±0.26	0.01±0.01	0.077	0.696	0.040*	0.145
LGN left volume	0.06±0.03	0.02±0.02	0.06±0.02	0.008**	0.946	0.012*	0.003**
LGN left volume %	0.01±0.03	0.08±0.08	0.01±0.01	0.080	0.666	0.041*	0.167
MGN total volume	0.13±0.04	0.06±0.06	0.15±0.01	0.037*	0.394	0.010*	0.001**
MGN total volume %	0.12±0.44	0.97±0.91	0.01±0.01	0.075	0.708	0.040*	0.185
MGN right volume	0.06±0.02	0.03±0.03	0.07±0.01	0.042*	0.347	0.009**	0.001**
MGN right volume %	0.08±0.32	0.70±0.66	0.01±0.01	0.075	0.708	0.040*	0.167
MGN left volume	0.06±0.01	0.02±0.03	0.07±0.01	0.035*	0.542	0.012*	0.001**
MGN left volume %	0.03±0.12	0.26±0.24	0.01±0.01	0.076	0.707	0.040*	0.320
CN total volume	0.25±0.07	0.12±0.13	0.28±0.02	0.070	0.393	0.023*	0.007**
CN total volume %	0.15±0.52	1.15±1.07	0.02±0.01	0.075	0.709	0.040*	0.119
CN right volume	0.12±0.03	0.05±0.06	0.13±0.01	0.046*	0.665	0.019*	0.006**
CN right volume %	0.13±0.46	1.01±0.95	0.01±0.01	0.075	0.706	0.040*	0.164
CN left volume	0.12±0.03	0.06±0.07	0.14±0.01	0.105	0.218	0.027*	0.008**
CN left volume %	0.02±0.05	0.13±0.11	0.01±0.01	0.074	0.734	0.040*	0.008**
MN total volume	1.23±0.41	0.50±0.59	1.36±0.28	0.020*	0.655	0.007**	0.001**
MN total volume %	0.21±0.46	1.09±0.95	0.09±0.02	0.080	0.717	0.042*	0.508
MN right volume	0.63±0.20	0.24±0.29	0.68±0.16	0.011*	0.825	0.005**	0.001**
MN right volume %	0.14±0.37	0.85±0.77	0.04±0.01	0.080	0.703	0.042*	0.523
MN left volume	0.60±0.21	0.26±0.31	0.67±0.12	0.040*	0.497	0.011*	0.001**
MN left volume %	0.06±0.09	0.23±0.18	0.04±0.01	0.080	0.778	0.045*	0.242
HN total volume	0.04±0.01	0.01±0.02	0.04±0.01	0.030*	0.993	0.021*	0.007**
HN total volume %	0.03±0.13	0.29±0.27	0.01±0.01	0.076	0.702	0.040*	0.129
HN right volume	0.02±0.01	0.01±0.01	0.02±0.01	0.028*	0.849	0.011*	0.002**
HN right volume %	0.01±.04	0.08±0.08	0.01±0.01	0.076	0.706	0.040*	0.114
HN left volume	0.02±0.01	0.01±0.01	0.02±0.01	0.033*	0.984	0.040*	0.016*
HN left volume %	0.02±0.09	0.20±0.19	0.01±0.01	0.076	0.700	0.039*	0.037*
MTN total volume	0.16±0.51	0.16±0.13	0.01±0.01	0.997	0.620	0.036*	0.006**
MTN total volume %	4.82±18.63	40.09±38.04	0.01±0.01	0.075	0.704	0.040*	0.003**
MTN right volume	0.15±0.517	0.15±0.14	0.01±0.01	0.999	0.616	0.038*	0.033*
MTN right volume %	4.81±18.59	40.02±37.97	0.01±0.01	0.075	0.704	0.040*	0.015*
MTN left volume	0.01±0.01	0.01±0.01	0.01±0.01	0.597	0.989	0.431	0.267
MTN left volume %	0.01±0.03	0.07±0.06	0.01±0.01	0.075	0.705	0.003*	0.005**
ISN total volume	3.58±1.24	1.78±1.96	4.03±0.53	0.087	0.487	0.026*	0.014*
ISN total volume %	2.71±9.44	20.59±19.26	0.28±0.03	0.075	0.708	0.040*	0.065
ISNright volume	1.74±0.76	0.84±1.02	1.98±0.32	0.110	0.612	0.029*	0.018*
ISN right volume %	0.12±0.05	0.06±0.07	0.14±0.02	0.122	0.653	0.038*	0.035*
ISN left volume	1.83±0.58	0.93±0.94	2.05±0.22	0.075	0.469	0.023*	0.006**
ISN left volume %	2.58±9.47	20.53±19.34	0.14±0.01	0.075	0.707	0.040*	0.071

RTT: Responsive to Treatment, TRE: Treatment-resistant, X±SD: Mean ± Standard Deviation, Asym: Asymmetry, LGN: Lateral Geniculate Nuclei, AVN: Anterior Ventral Nuclei, MGN: Medial Geniculate Nuclei, VAN: Ventral Anterior Nuclei, CN: Centromedian Nuclei, VLAN: Ventral Lateral Anterior Nuclei, MN: Mediodorsal Nuclei, VLPN: Ventral Lateral Posterior Nuclei, HN: Habenular Nuclei, VPLN: Ventral Posterior Lateral Nuclei, MTN: Mammillothalamic Tract Nuclei, PN: Pulvinar Nuclei, ISN: Intermediate Space Nuclei. **: p<0.01. *: p<0.05.

DISCUSSION

Brain volume measurements in schizophrenia have been widely studied; however, this research is among the first to compare volumes between treatment-responsive and treatment-resistant patients. The study provides important insights into structural brain changes associated with treatment outcomes. The findings highlight the potential of volumetric brain measurements as markers for understanding the neurobiological basis and clinical characteristics of schizophrenia. Notably, treatment-resistant patients exhibited significant volume reductions in regions such as the frontal and parietal lobes and thalamic nuclei when compared to both healthy controls and treatment-responsive individuals (Nakajima et al., 2015). These results support the hypothesis that treatment resistance is linked to more severe neuroanatomical abnormalities, likeliy reflecting intensified neurodevelopmental and neurodegenerative processes.

This study revealed that schizophrenia patients who did not respond to treatment exhibited significantly higher PANSS negative total scores and BPRS values compared to those who responded to treatment. These findings underscore the critical role that negative symptoms and overall psychiatric symptom severity play in the clinical trajectory of schizophrenia, particularly regarding treatment outcomes. As assessed by the PANSS, negative symptoms encompass deficits in emotional expression, motivation, and social engagement, all of which profoundly impact a patient's quality of

life and functional capacity. The higher PANSS negative total scores observed in treatment-resistant patients suggest that these individuals are more burdened by these symptoms, which may contribute to their lack of responsiveness to standard therapeutic interventions (Melzer-Ribeiro et al., 2024). Negative symptoms are notoriously difficult to treat and are often less responsive to antipsychotic medications, which are primarily effective in addressing positive symptoms such as delusions and hallucinations (Correll & Schooler, 2020). This resistance to treatment was indicative of underlying neurobiological differences that predispose specific individuals to a more severe and persistent symptom profile.

The elevated BPRS values in treatment-resistant patients further highlight the complexity of their clinical presentation. The BPRS, which measures the severity of various psychiatric symptoms, including depression, anxiety, and psychosis, provides a comprehensive overview of a patient's symptom burden (Iasevoli et al., 2018). Higher BPRS scores in treatment-resistant indicate a more severe and pervasive psychiatric condition, which may be resistant to conventional treatments due to the presence of more pronounced or refractory symptoms. This could also reflect a more global impairment clinically and maybe also neuroanatomically in these patients, encompassing positive and negative symptoms and affective and cognitive disturbances.

In this study, we conducted a detailed analysis of brain volume measurements in schizophrenia patients and healthy controls. The results revealed significant differences in several key brain regions, including WM, GM, cortical GM, total brain GM and WM, cerebellar GM, IC, Cerebellum total, Cerebellum GM total, and various cerebral subregions. These findings contribute to the growing body of evidence highlighting the neuroanatomical alterations associated with schizophrenia, particularly in treatment responsiveness, reflecting a variety of clinical symptoms. While most studies in the literature have reported reduced GM, WM, and cerebellar volume in schizophrenia patients (Deniz et al., 2024; He et al., 2019; Kim et al., 2020; Tronchin et al., 2020), a few studies have found no significant difference (van der Velde et al., 2015). The observed reductions in WM and GM volumes among treatment-resistant schizophrenia patients, compared to both healthy controls and treatment-responsive patients, align with previous research indicating widespread structural abnormalities in this population. These findings support the involvement of both neurodevelopmental and neurodegenerative processes in the disorder. Reductions in total brain GM and WM volumes, as well as in specific regions such as the cerebellum and cerebrum, suggest that schizophrenia involves both global and regional brain atrophy and may represent a network disorder affecting multiple brain areas over time. A key finding of this study is the significant difference in brain volumes between treatment-responsive and treatment-resistant patients, with the latter exhibiting more pronounced volume reductions across several regions, including the total cerebrum, left cerebrum, and their corresponding GM and WM components. These results indicate that treatment resistance may be linked to more extensive or severe neuroanatomical changes. Notably, reductions in cerebellar GM and IC volumes were especially prominent in treatment-resistant. Traditionally associated with motor control, the cerebellum has increasingly been recognized for its role in cognitive and affective processes (Schmahmann, 2019). Reduced cerebellar GM in treatment-resistant may contribute to the cognitive deficits often observed in treatment-resistant schizophrenia, including impairments in executive function, working memory, and emotional regulation. Similarly, reductions in IC volume, encompassing the total cranial cavity, could reflect broader structural deficits that impact overall brain function. This study corroborates previous findings in the literature, demonstrating that CSF volumes are significantly increased in patients with schizophrenia compared to healthy controls (Deniz et al., 2024; Orlovska-Waast et al., 2019). Notably, this increase in CSF was even more pronounced in schizophrenia patients who did not respond to treatment, suggesting that elevated CSF volumes might be reflecting neurodegeneration and treatment resistance.

The observed reductions in the volumes of the frontal lobe, triangular inferior frontal gyrus, middle frontal gyrus, temporal lobe, fusiform gyrus, planum polare, superior temporal gyrus, parietal lobe, postcentral gyrus, and precuneus in schizophrenia patients who did not respond to treatment are noteworthy. These findings align with previous research suggesting that structural brain abnormalities are more pronounced in treatment-resistant schizophrenia (He et al., 2019; Kim et al.,

2020; Tronchin et al., 2020). The frontal and temporal regions, critical for cognitive functions such as decision-making, memory, and social behavior, show significant atrophy, potentially contributing to the persistence of symptoms in these patients. The involvement of the fusiform gyrus and planum polare, areas associated with visual processing and auditory functions, further underscores the multifaceted impact of schizophrenia on brain structure. The parietal lobe, particularly the postcentral gyrus and precuneus, plays a vital role in sensory processing and self-referential thought, and its reduced volume relates to the cognitive and perceptual disturbances observed in treatment-resistant schizophrenia. These volumetric reductions reflect a more severe neurodevelopmental disruption in patients who do not respond to conventional treatments, highlighting the need for tailored therapeutic approaches for this subgroup.

Previous research has consistently reported significant thalamic volume reductions in individuals with schizophrenia (Dönmezler et al., 2024). This study is among the first to provide a detailed analysis of thalamic nuclei in this population. Findings revealed that treatment-resistant schizophrenia patients exhibited significantly lower volumes in multiple thalamic regions, including the total thalamus and bilateral LGN, AVN, MGN, VAN, CN, VLAN, MN, VLPN, HN, VPLN, PN, and ISN nuclei. These structural deficits suggest that the thalamus (essential for sensory, motor, and cognitive processing) may be particularly compromised in patients who do not respond to standard treatments. Thalamic atrophy correlates with higher PANSS negative symptom scores, indicating a link between thalamic abnormalities and the severity of negative symptoms such as reduced emotional expression, motivation, and social engagement. These volumetric reductions may disrupt key neural circuits, contributing to persistent symptoms and poor treatment response. The findings underscore the need for therapeutic strategies that specifically target thalamic dysfunction and highlight the value of incorporating neuroanatomical assessments into the clinical management of treatment-resistant schizophrenia.

This study presents several strengths that enhance its contribution to understanding schizophrenia and treatment resistance. It is among the first to comprehensively compare brain volumes between treatment-responsive and treatment-resistant patients, offering essential insights into neuroanatomical differences related to treatment outcomes. The detailed analysis of multiple brain regions advances knowledge of structural abnormalities associated with resistance to treatment. Additionally, integrating clinical symptom scales, such as the PANSS and BPRS, with neuroimaging data provides a more comprehensive understanding of the relationship between brain structure and symptom severity. However, the study has limitations. Its cross-sectional design limits the ability to establish causality, making it unclear whether brain volume reductions are a cause or consequence of treatment resistance. Furthermore, all patients were on antipsychotic medications, including various atypical agents such as olanzapine, risperidone, amisulpride, aripiprazole, clozapine, paliperidone, and quetiapine. Previous research suggests that antipsychotic use may influence brain volume, potentially contributing to the observed structural changes (Kanahara et al., 2022; Roiz-Santiañez et al., 2015).

Additionally, the study's sample size, while sufficient for detecting significant differences, may limit the generalizability of the findings to broader schizophrenia populations. Future research should consider longitudinal designs with larger, more diverse samples to validate and extend these findings. Furthermore, while the study provides significant insights into structural brain changes, it does not explore the functional implications of these volumetric reductions, which could be addressed through complementary imaging techniques such as functional MRI.

Conclusion

In conclusion, this study is among the first to conduct a comprehensive comparison of brain volumes between treatment-responsive and treatment-resistant schizophrenia patients, offering essential insights into structural brain alterations associated with treatment outcomes. The findings demonstrate significant volume reductions in treatment-resistant individuals across multiple brain regions, including the frontal and parietal lobes, thalamic nuclei, and cerebellum, relative to healthy controls and treatment-responsive patients. These results support the notion that treatment resistance is associated with more severe neuroanatomical abnormalities, potentially reflecting advanced neurodevelopmental or neurodegenerative

processes. The correlation between higher PANSS negative scores and elevated BPRS values in treatment-resistant further underscores the role of negative symptoms and overall symptom severity in treatment resistance. In particular, thalamic atrophy plays a critical role in persistent negative symptoms. These findings highlight the potential of brain volumetric measurements as biomarkers for predicting treatment response and guiding personalized therapeutic strategies. Future longitudinal studies are needed to clarify the causal relationship between structural changes and treatment outcomes and to explore their functional implications.

Declarations

Funding: Not applicable.

Conflict of Interest

There is no conflict of interest to declare.

Ethics approval

This research complied with the principles of the Helsinki Declaration and with ethical approval from the Atatürk University Medical Ethics Committee meeting numbered B.30.2.ATA.0.01.00/805, dated October 26, 2023.

Code Availability: Not applicable.

Author Contributions

Research Design, HÖ., GD., NK.; Research Data Input, GD., NA., HÖ., NK.,; Statistical Data Analysis, GD., NA., HÖ., NK.,; Data Processing, GD., NA., NK.; Manuscript Preparation, GD., NA., HÖ., NK. ; Journal Literacy, GD., NA., HÖ., NK.,. Each author has reviewed the final draft of the manuscript and given their approval.

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