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Investigating The Brain Regions Related to Early Onset Psychosis: A Voxel-Based Morphometry Study Considering The Effect of Hereditary Burden and Environmental Risk Factors

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ABSTRACT

Introduction: Schizophrenia is both a neurodevelopmental and neurodegenerative disorder that manifests a complex spectrum of symptoms, significantly impacting mental health. In early-onset psychosis, similar to adult studies, neuroimaging focuses on ventral prefrontal cortical areas and posterior temporoparietal regions, crucial for understanding the neurodevelopmental mechanisms of these conditions in such drug-naive patients. This enables magnetic resonance imaging to be acquired before significant neurodegenerative changes occur, in contrast to chronic schizophrenia cases. Therefore, our study helps advance understanding of disease mechanisms in this patient population.

Methods: We recruited forty-one subjects (17 females, 24 males; mean age=16 years; age range: 12–17 years) who were diagnosed with first-episode psychosis (FEP). We examined the relationship between gene and environmental risk scores (GERS) and whole-brain gray matter (GM) volumes through voxel-based morphometry (VBM).

Results: We found a positive correlation between GM volumes of the left medial frontal gyrus, right anterior prefrontal cortex, left superior frontal gyrus, left operculum of the inferior frontal gyrus, left superior parietal lobe, and left supramarginal gyrus with the GERS. We found a negative correlation between GM volumes of the left superior frontal gyrus, left cerebellum, and the GERS.

Conclusion: Our findings contribute to the understanding of structural abnormalities associated with schizophrenia, aligning with existing literature highlighting GM changes in frontal, parietal, and temporal cortices, as well as limbic structures. Our study underscores the importance of integrating structural and functional neuroimaging approaches to elucidate the pathophysiology of early-onset schizophrenia, emphasizing regions like the dorsolateral prefrontal cortex, ventrolateral prefrontal cortex, and posterior parietal areas.

Keywords: Child psychiatry, first-episode psychosis, gray matter volume, neuroimaging, voxel-based morphometry

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INTRODUCTION

Schizophrenia, characterized by neurodevelopmental features at onset and neurodegenerative features as it progresses, presents a complex spectrum of positive and negative symptoms that significantly impact global psychiatric health (1). Despite typically emerging in early adulthood, schizophrenia can also manifest at a younger age in a subset of patients referred to as early-onset schizophrenia, distinguished by the onset of symptoms before the age of 18. It has been demonstrated that genetic and environmental factors play a pronounced role in early-onset cases compared to those patients with a later onset (2). Indeed, the etiological foundations of psychosis spectrum disorders that have been explored through family, twin, and adoption studies suggest that schizophrenia is likely inherited in a non-Mendelian, polygenic manner and is associated with a multifactorial etiology. Therefore, the genetic

Highlights

- **Schizophrenia is both a neurodevelopmental and neurodegenerative disorder.**
- **FEP studies are vital for understanding the disorder's neurodevelopmental basis.**
- **A hereditary burden and environment risk score was introduced for the first time.**
- **In line with the literature, prefrontal, and posterior parietal regions were shown.**

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predisposition is significantly influenced by environmental factors, including socioeconomic status, nutritional deficiencies, perinatal complications, urban or rural residency, and exposure to various toxins or infections (3). As a result, an enhanced understanding of the gene-environment interactions in schizophrenia is vital for improving both diagnostic and therapeutic approaches, particularly in early-onset cases.

Neuroimaging genomic studies aim to identify the neurophysiological correlates of specific genes. However, the polygenic and multifactorial nature of most psychiatric disorders complicates definitive outcomes (4). Nonetheless, recent research has identified several morphological and functional cerebral alterations that could serve as biomarkers for conditions considered 'at-risk' for schizophrenia, thereby promising early preventative interventions (5).

Regarding early onset psychosis, neuroimaging studies, akin to those in adults, often focus on the ventral prefrontal cortical areas such as the dorsolateral prefrontal cortex in adults, and the posterior temporoparietal regions (6). Arsalidou et al. (2020) noted in their review of 16 meta-analyses that, the cortical regions in early-onset psychosis patients showed significant activity changes in the ventrolateral prefrontal cortex, often in the hemisphere opposite to that observed in adults (7). This discrepancy might be attributed to the incomplete maturation of the adolescent prefrontal cortex and the fact that most subjects in these studies are in the acute phase of their first psychotic episode and are receiving antipsychotic medications. Research on early-onset schizophrenia is crucial for elucidating the neurodevelopmental pathophysiology of these complex disorders, particularly as these studies often involve first-episode, drug-naive patients, allowing for MRI scans before neurodegenerative changes become prominent, unlike in chronic schizophrenia cases (7). Therefore, our study is particularly important for elucidating the pathophysiology of the disease in this patient population.

To date, no neuroimaging study has calculated and utilized a polygenic gene-environment score to detail the multifactorial etiology of schizophrenia. A limited number of child and adolescent voxel-based morphometry (VBM) studies have stratified genetic risk by dividing patients into groups based on their familial proximity to the disease and family history (8). In our study, the genetic and environmental risk score (GERS) was calculated to determine the effect of family history and environmental factors in an intertwined and more sophisticated way. Large-sample genotype studies have been used to estimate the genetic effect from patient databases in countries such as Denmark, Estonia, Sweden, and Switzerland (9). In addition, the effect of the percentage of environmental risk factors was included in the calculation to get a more accurate risk score. In this way, the combined effect of genetic and environmental factors could be better assessed.

It was found that the presence of schizophrenia history in siblings and parents increases the risk by 10%, the grandparents increase the risk by approximately 5%, and a history of disease in aunt, uncle, and first cousins increases the risk by about 2% (9).

Apart from this, having a family history of bipolar disorder also increases the risk of schizophrenia, and a history of bipolar disorder in first-generation relatives increases the risk of schizophrenia by an average of 6.3%. In our study, patients with a history of bipolar disorder in their first, second, and third-generation relatives were also considered and included in the calculation (10). Although the presence of autism, anxiety disorders, and depressive disorders in the family also increases the risk of schizophrenia, the genetic burden of these disorders was found to be less than 1%, so they were not included in the calculation. (11).

Interestingly, studies investigating various mechanisms have shown that sharing the same environment with relatives who have a history of schizophrenia—most likely through its impact on healthy attachment and care, especially if the primary caregiver has a history of the disease—can increase the risk. Additionally, growing up in an environment with a similar socioeconomic level and being exposed to similar infections or neurotoxins also raises the risk by approximately 10% (3). Substance use is one of the most important known environmental risk factors, and there are widespread studies on the fact that cannabis and its derivatives trigger the disease progress or set back the onset age. According to Buckley et al. (2009), exposure to cannabis and other substances increases the risk of schizophrenia by 6% (12).

The current study aims to calculate and estimate a GERS for use in VBM analysis of child and adolescent first-episode psychosis patients to identify brain regions correlated with early onset schizophrenia.

METHOD

Participants

The Ethics Committee for Medical Studies of Istanbul Bakirkoy Dr. Sadi Konuk Research and Training Hospital approved the study protocol (Dated 04.01.2022/Protocol no: 572). Forty-one subjects (17 females, 24 males; mean age: 16 years; age range: 12–17 years) from Istanbul Bakirkoy Mazhar Osman Mental Health and Neurological Diseases Education and Research Hospital Child and Adolescent Emergency Psychiatric Clinic were included in the study who were diagnosed with first-episode psychosis (FEP) according to DSM-5. Then, two psychiatrists (MCE and DK) interviewed all participants using the Turkish version of the Kiddie Schedule for Affective Disorders and Schizophrenia– Present and Lifetime Version (KSADS-PL) to exclude the participants with a psychiatric history and comorbid psychiatric disorders (13). Exclusion criteria were (a) participants presenting with an affective disorder diagnosis according to the Diagnostic and Statistical Manual of Mental Disorders -5 (DSM-5), (b) having a premorbid diagnosis of intellectual disability, and (c) having a premorbid diagnosis of autism spectrum disorder. The history obtained from the patients' families, the feedback from their teachers, and the examination of any available archive records have been used to rule out the diagnoses of premorbid intellectual disability and/or autism spectrum disorder. The kurtosis and skewness values of the patient's age, education level, and socioeconomic level show that the data is normally distributed. In addition, all participants were given detailed information about the study and provided signed written informed consent from their parents before participating in the study.

Study Design and Tools

This study employs a cross-sectional design to investigate the relationship between genetic and environmental risk factors and brain morphology in child and adolescent first-episode psychosis patients. The primary aim is to calculate and estimate a GERS for use in VBM analysis to identify brain regions associated with early-onset schizophrenia.

The sample consists of 41 participants aged 12 to 17 years. Data were collected through direct hospital visits of first-episode psychosis patients as well as from archived medical records. The diagnosis of first-episode psychosis was confirmed by the psychiatric specialists of the research team. Brain imaging data were acquired using magnetic resonance imaging (MRI) scans, focusing on identifying structural abnormalities correlated with psychosis onset. The GERS was computed by summing the hereditary risk factors identified through family history of psychiatric disorders. Environmental factors, when available, were included to provide a comprehensive risk profile for each patient.

VBM was performed using the SPM12 software to analyze the MRI data. This technique allowed for an unbiased, whole-brain analysis of gray matter (GM) volume differences across the sample, facilitating the detection of brain regions associated with the calculated GERS values.

• MRI Scanner: Used to obtain high-resolution structural brain images.

• SPM12 Software: Employed for VBM analysis to assess GM volume.

• Clinical assessment by consultant psychiatrists: The consultant psychiatrists from the research team diagnosed first-episode psychosis using standardized clinical criteria.

• Patient records and archival data: Additional clinical data, including family history, were collected from hospital archives to estimate the GERS.

Calculating a Gene and Environmental Risk Score in Patients with First-Episode Psychosis

Based on the aforementioned literature in introduction, we calculated a hereditary burden and environmental risk score to stratify the schizophrenia risk of our patient population. To calculate the family burden and environmental impact, we conducted individual interviews with each participant to assess key factors. These included the presence of substance use, whether the participant was raised in an environment with someone diagnosed with a psychiatric disorder, specifically schizophrenia, bipolar disorder, or depression. Each of these variables was assigned a corresponding value based on established literature. Using this data, we created a risk matrix to quantify the overall family burden and environmental impact for each participant. (Table 1). This approach has allowed us to incorporate the interplay between genetic and environmental factors in the development of schizophrenia.

Magnetic Resonance Imaging (MRI) Data Acquisition

MRI data was acquired within the first week after initiating the first antipsychotic treatment.

Structural imaging was performed on a 1.5 T Siemens Magnetom Area MR scanner equipped with a 20-channel head matrix coil (Siemens, Magnetom Area, Erlangen, Germany). The data acquired were axial TSE T2 sequences (TR/TE: 4810/102 msn, slice number: 23, slice thickness: 5 mm voxel size: 0.8 × 0.8 × 5 mm Fov: 260, Nex1, GRAPPA factor: 2) with BLADE technique, coronal 3D SPACE Dark Fluid (FLAIR) (TR/TE: / TI: 9050/82/1800 msn, slice number: 21, slice thickness: 5 mm, voxel size: 0.8 × 0.8 × 5 mm, FoV: 260, Nex: 1 GRAPPA factor: 2) sequences and sagittal T1 3D MP-RAGE (TR/TE: /TI: 2400/2.48/900 msn, slice number: 160, slice thickness: 1.2 mm, voxel size: 1.3 × 1.3 × 2 mm, FoV: 240, Nex: 1 GRAPPA factor: 2) sequences. T2 weighted TSE and DARK Fluid (FLAIR) sequences were used for detecting any patients with cortical abnormality or intracranial lesions, and 3D T1 weighted MP-RAGE sequences were used for GM calculations.

Voxel-based morphometry (VBM) Data Processing

We performed VBM analysis using the CAT12 toolbox (Wellcome Department of Cognitive Neurology; http: //dbm. neuro. uni-jena. de/cat12) in SPM12 (Statistical Parametric Mapping, Welcome Trust Centre for Neuroimaging, http: //www. fil. ion. ucl. ac. uk/spm) implemented in MATLAB R2019b. First, we transformed DICOM files to NIFTI format via SPM12. The anatomical images were manually reoriented as the anterior commissure coordinate matched the origin point (0,0,0) in MNI (Montreal Neurological Institute) space. Next, data preprocessing was performed using SPM12 CAT12 via the pipeline based on recommendations for standardized VBM analysis (14). All images were segmented into GM, white matter, and cerebrospinal fluid. All preprocessed scans appeared to be of good-to-excellent quality based on CAT12 toolbox ratings of image

Table 1. Gene and environmental risk score table

Participants	Schizophrenia risk score	Bipolar risk score	Other psychiatric disorder risk score	Environmental risk score (living together)	Substance use score	Total score
Subject 1	10%	2%	-	10%	-	22%
Subject 2	10%	-	-	10%	-	20%
Subject 3	10%	-	-	10%	-	20%
Subject 4	5%	-	-	10%	-	15%
Subject 5	12%	-	-	10%	-	22%
Subject 6	12%	-	-	10%	-	22%
Subject 7	2%	6%	-	10%	-	18%
Subject 8	10%	6%	-	10%	-	26%
Subject 9	15%	-	-	10%	-	25%
Subject 10	5%	-	-	10%	-	15%
Subject 11	5%	-	-	-	6%	11%
Subject12	5%	-	-	-	-	5%
Subject 13	-	-	<1%	-	-	<1%
Subject 14	-	3%	-	-	-	3%
Subject 15	2%	-	-	-	-	2%
Subject 16	5%	-	-	-	-	5%
Subject 17	-	6%	-	-	-	6%
Subject 18	2%	-	-	10%	-	12%
Subject 19	<1%	-	-	-	-	<1%
Subject 20	-	-	<1%	-	-	<1%
Subject 21	2%	-	-	-	-	2%

* The participants who had zero gene and environmental risk score was not addressed at this table.

data quality, so the data of all forty-one participants had passed through an automated quality-check protocol. None of the participants needed to be excluded due to the quality of their imaging data. All images were then normalized to standard MNI space and smoothed with an 8 mm kernel via SPM12 CAT12.

Statistical Analysis

We used SPSS 26.0 (IBM Corp. Released 2019. IBM Statistical Package for Social Sciences (SPSS), version 26.0 Armonk, NY: IBM Corp) for statistical analysis of the patient's sociodemographic (age, gender, education and income level) variables. We evaluated the relationship between GERS and whole-brain GM volumes with multiple regression analysis in CAT12 toolbox: VBM-basic models. All GERS scores and GM volumes were checked for data cleaning, and outliers were dismissed thoroughly. The smoothed GM images and GERS scores were submitted as factors, and total intracranial volume was added as a covariate. For region of interest (ROI) analyses bilateral dorsolateral prefrontal cortex, ventrolateral prefrontal cortex, posterior temporoparietal regions including superior temporal cortex and inferior parietal cortex, insula and cerebellum were identified using the Wake Forest University PickAtlas Toolbox, which generating ROI masks based on the Talairach Daemon database. The cluster-level threshold of 40 voxels at uncorrected $p<0.001$ were set for the statistical analysis. The uncorrected $p<0.001$, with the a priori hypothesis present, was approximately equivalent to $p<0.05$ corrected for multiple comparisons.

RESULTS

The age, education, and income levels were similar among female and male subjects ($p>0.05$).

The calculated gene and environmental risk score for each subject is shown in Table 1; the participants who had zero GERS score were not addressed on the table. The highest and lowest gene and environmental risk scores were 22% and 0%, respectively. Ten of the participant's risk score was 0%.

We found a positive correlation between the left medial frontal gyrus, right anterior prefrontal cortex, left superior frontal gyrus, left operculum (part of inferior frontal gyrus), left superior parietal lobe and left supramarginal gyrus GM volumes and the GERS (Figure 1). A negative correlation was also found between the left superior frontal gyrus, left cerebellum GM volumes, and the GERS (Figure 2). The t-values, p-values, voxel sizes, and MNI coordinates of the regions that were related to the GERS are shown in Tables 2 and 3.

DISCUSSION

In our study, we observed a positive correlation between the GM volumes of the left superior and medial frontal gyrus, right anterior prefrontal cortex, left operculum part of the inferior frontal gyrus, left superior parietal lobe, and supramarginal gyrus, and the GERS. Conversely, a negative correlation was found between the GM volumes of the left superior frontal gyrus and left cerebellum and the GERS.

Neuroimaging studies on schizophrenia primarily involve comparisons between high-risk individuals, first episode or chronic patients, with healthy controls (15). Other research includes longitudinal studies showing gray matter volume or functional changes over time, and twin studies to explore the genetic basis of the disease (16). Recent literature primarily focuses on fMRI studies demonstrating altered brain connectivity linked to various cognitive or executive symptoms (6). These functional studies often target the dorsolateral prefrontal cortex (DLPFC), ventrolateral prefrontal cortex (VLPFC), and posterior parietal regions (7). Early-onset schizophrenia literature often highlights ventral prefrontal and posterior parietal areas, unlike adult studies emphasizing

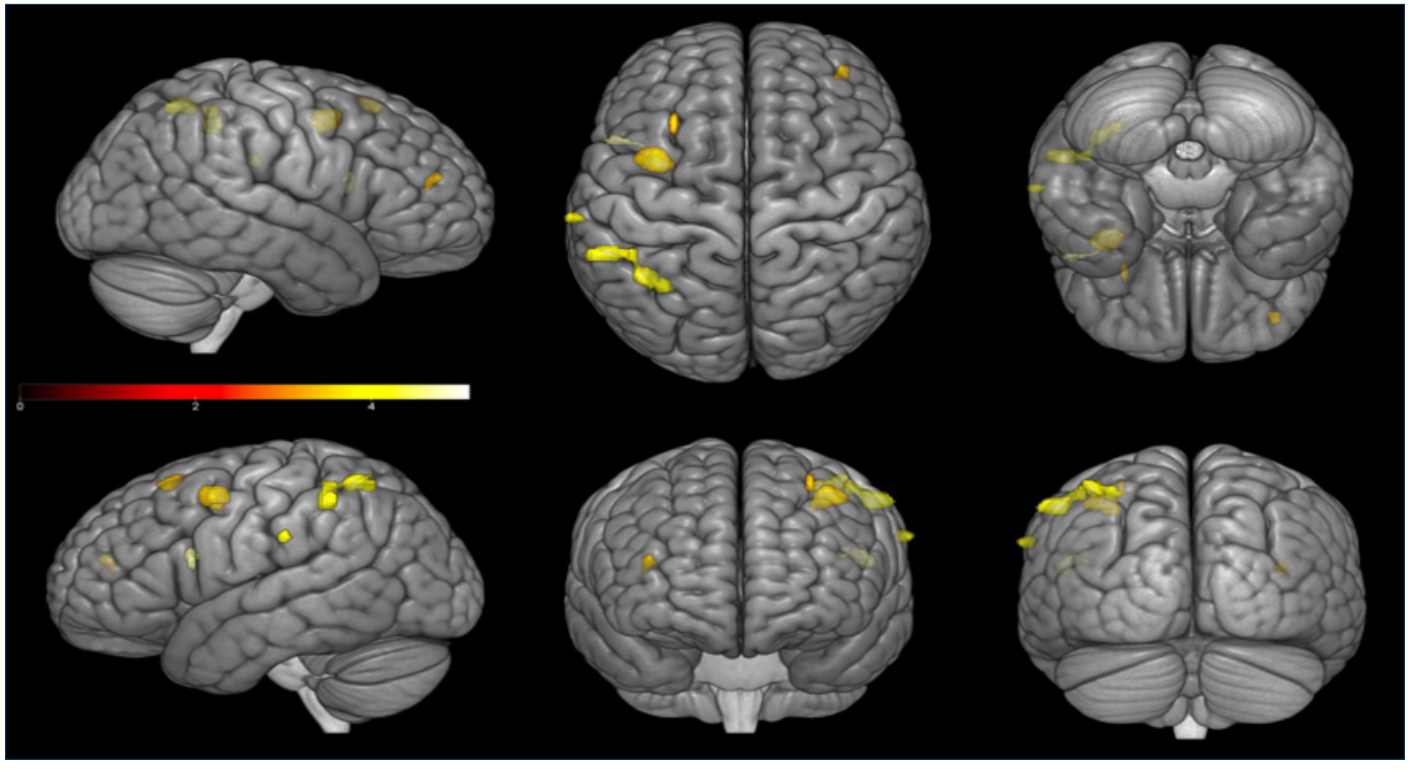

Figure 1. The brain regions positively correlated with the gene and environment risk score, including left medial frontal gyrus, right anterior prefrontal cortex, left superior frontal gyrus, left operculum (a part of inferior frontal gyrus), left superior parietal lobe and left supramarginal gyrus, are shown on the left.

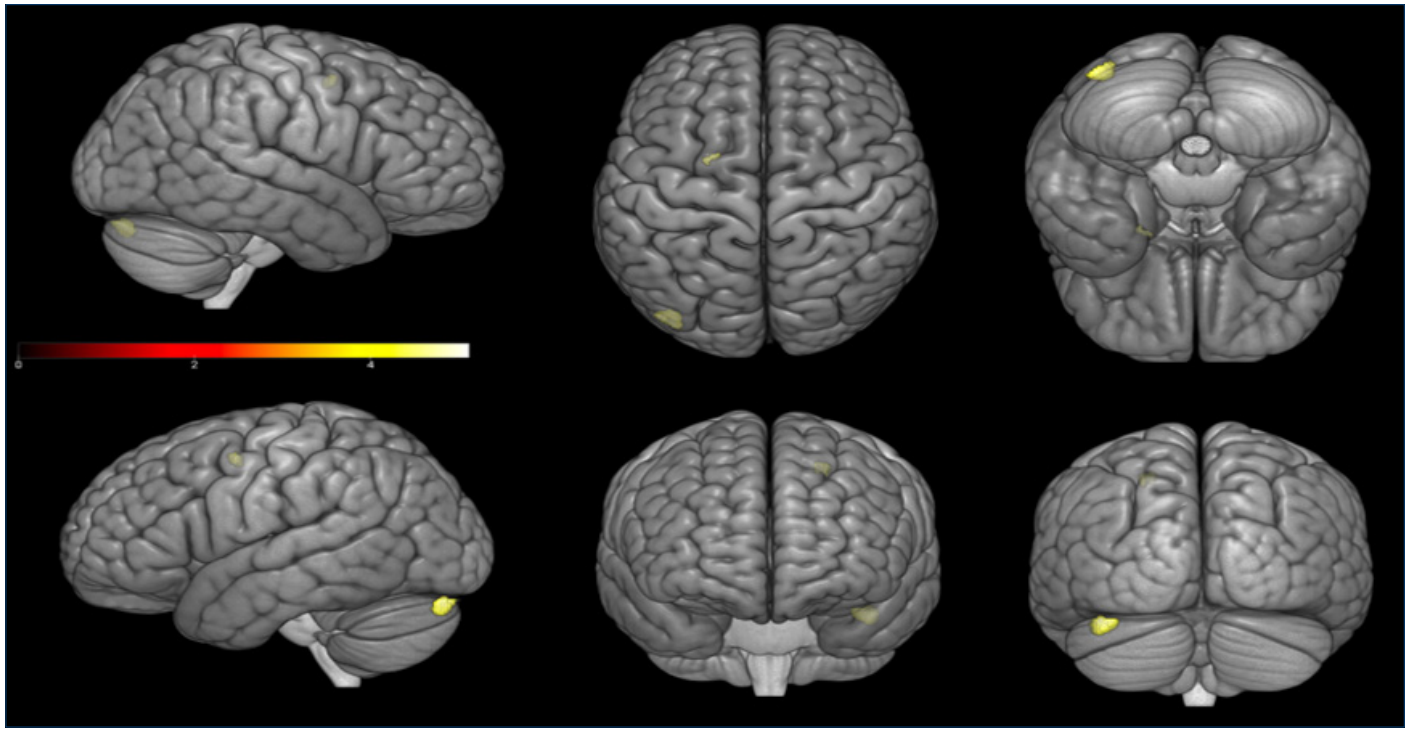

Figure 2. The brain regions negatively correlated with the gene and environment risk score, including the left superior frontal gyrus and left cerebellum, are shown on the left.

Table 2. Brain regions showing positive correlation with gene and environment risk score

Region (BA)	t-value	p-value	Cluster size	MNI coordinates		
				x	y	z
L medial prefrontal gyrus (6)	5.16	<0.001	319	-33	0	50
R anterior prefrontal cortex (10)	3.86	<0.001	51	36	46	18
L superior frontal gyrus (8)	3.85	<0.001	56	-27	24	56
L operculum (44) (inferior frontal gyrus)	3.81	<0.001	82	-51	14	18
L superior parietal gyrus (40)	4.49	<0.001	428	-39	-52	57
L supramarginal gyrus (40)	3.68	<0.001	50	-64	-24	30

BA: Brodmann area; L: left; MNI: Montreal Neurological Institute; R: right.

Table 3. Brain regions showing negative correlation with gene and environment risk score

Region (BA)	t-value	p-value	Cluster size	MNI coordinates		
				x	y	z
L superior frontal gyrus (6)	3.96	<0.001	41	-20	0	50
L cerebellum	3.99	<0.001	148	-39	-86	-24

BA: Brodmann area; L: left; MNI: Montreal Neurological Institute; R: right.

dorsal prefrontal and frontal regions. This difference is attributed to the incomplete maturation of the adolescent prefrontal cortex and the acute phase of psychosis often seen in early-onset cases (7).

Structural studies in schizophrenia have identified GM abnormalities in the frontal, parietal, superior temporal, anterior cingulate cortices, and limbic system (16). The disease progresses with decreased thalamic volume (17). In high-risk patients, more significant GM loss is observed in those who develop psychosis, suggesting these regions are linked to disease progression. However, no specific region has yet been definitively identified as a biomarker for high-risk individuals.

Research on early-onset schizophrenia is limited due to the rarity of the disease in children and adolescents and ethical/legal restrictions on neuroimaging in this vulnerable group (18). Recent meta-analyses have included small studies using structural and functional imaging to analyze early-onset patient data (19). Despite limited data, Ioakeimidis et al. (2020) emphasized the importance of structural studies in early-onset schizophrenia but did not find significant GM volume changes. Therefore, our study might contribute to the literature, potentially aiding future meta-analyses in achieving statistically significant results.

The left medial frontal gyrus is linked to executive functioning, consistently impaired in schizophrenia, with structural changes correlating with illness duration (20). A follow-up study of first-episode psychosis in children and adolescents showed reduced left medial frontal volume in both bipolar and schizophrenia patients after one year (21). Contrarily, a meta-analysis by (15) found increased left medial frontal gyrus volume in high-risk individuals, possibly due to neuroinflammation or compensatory mechanisms (22). Vogeley et al. (2000) reported increased right prefrontal cortical volume in postmortem studies, potentially due to a disturbed gyrification index (GI) (23). Harris et al. (2007) also noted a higher prefrontal GI in high-risk patients who developed schizophrenia (24).

The right anterior prefrontal cortex is involved in complex problem-solving and planning (25). Our study showed increased volume in this area, in line with findings by Stanfield et al. (2007), who reported a higher GI in at-risk adolescents with schizotypal features and cognitive impairments (26). Moreover, the left superior frontal gyrus GM volume was found to be statistically different in concordance with GERS score. The left superior frontal gyrus is known to be involved in numerous cognitive and motor tasks. It has been highlighted in several functional MRI studies aimed at understanding the pathophysiological mechanisms in early-onset drug-naïve schizophrenia and identifying reliable biomarkers (27).

Ding et al. (2019) conducted a study involving 44 drug-naïve first-episode patients, 42 unaffected siblings of schizophrenia patients, and 44 healthy controls (27). They concluded that compared to healthy controls, both patients with schizophrenia and unaffected siblings exhibited enhanced global functional connectivity (GFC) in the left superior frontal gyrus. Furthermore, ROC analysis indicated that increased GFC in this region could effectively distinguish patients or siblings from controls with acceptable sensitivity. This study suggested that heightened GFC in the left superior frontal gyrus might serve as a potential endophenotype for schizophrenia. In our study, the observed changes in gray matter volume (both increases and decreases) may reflect the enhanced GFC reported in Ding et al. (2019), thereby providing further support for considering the left superior frontal gyrus as a potential endophenotype. Inferior frontal gyrus (IFG), which includes the pars opercularis, pars triangularis, and pars orbitalis, is associated with the VLPFC, as evidenced by studies that integrate both structural and functional data (28). As if emphasizing the importance of the relationship between structural and functional studies, this finding underscores the findings across these brain regions in the literature.

The left supramarginal gyrus and left superior parietal lobe, part of Brodmann area 40, are linked to higher social and cognitive functions, including self-other distinction, sensorimotor integration, language, emotions, and reflection (29). Functional meta-analyses on early-onset schizophrenia emphasize posterior parietal regions over prefrontal cortex changes, contrary to adult studies (7). Some follow-up studies have shown reversed brain asymmetry and decreased GM in the left supramarginal gyrus (30). Therefore, our findings align with these studies, showing gray matter volume increases in posterior regions correlated with GERS.

One of our limitations is that our patient population was relatively small, although comparable to other VBM studies that included a significant number of patients. We controlled for the potential confounding effects of antipsychotics on gray and white matter by limiting MRI scans to the first week after starting treatment; however, some patients were not able to be scanned at their initial admission. Furthermore, the absence of a control group in the study represents another limitation.

In conclusion, while many long-term studies typically report GM loss in schizophrenia, our study instead found increases in GM volume, possibly indicating heightened gyrification in early-onset patients (23). This highlights our contribution to the sparse data on early-onset psychosis, emphasizing neurodevelopmental aspects prior to the prominence of neurodegeneration. Additionally, we introduce a polygenic gene and environmental risk score which could be further refined and applied in future research. Furthermore, some structural imaging studies can delineate functional brain regions such as the DLPFC and VLPFC (28). Specifically, our findings of increased gray matter volume in the inferior frontal gyrus support existing functional MRI literature on the VLPFC (7). Further extensive studies are necessary to validate these brain regions as potential biomarkers for early-onset schizophrenia.

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Ethics Committee Approval: The Ethics Committee for Medical Studies of Istanbul Bakirkoy Dr. Sadi Konuk Research and Training Hospital approved the study protocol (Dated 04.01.2022/Protocol no: 572).

Informed Consent: All participants were given detailed information about the study and provided signed written informed consent from their parents before participating in the study.

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