HSPI The Open Access Publisher

JNND ISSN 2639-3220 JOURNAL OF NEUROSCIENCE AND NEUROLOGICAL DISORDERS

Research Article

Comparative Study of Cerebral Volumetric Variations in Patients with Schizophrenia with their Unaffected First-degree Relatives, using Magnetic Resonance Imaging Technique, a Case-control Study

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Abstract

Background and purpose: Schizophrenia (SZH) is a chronic mental disorder affecting the individuals` thoughts, perceptions, emotions, and behaviors. People with SZH may experience a wide range of positive, negative, and cognitive symptoms. Since there are no laboratory assays for definite SZH diagnosis, the authors aimed to identify the cerebral volumetric variations in SZH patients with the most prevalent positive symptoms as a diagnostic tool.

This study selected 15 SZH patients displaying the most prevalent positive symptoms based on the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) criteria. Assessment tools included the Mini-Mental State Examination (MMSE) for cognitive impairment, the Positive and Negative Syndrome Scale (PANSS) for symptom evaluation, and the Wechsler Intelligence Scale (WIS) for intelligence assessment. Additionally, 15 Healthy Controls (HC) without cerebral pathologies were recruited. T1w MRI images underwent analysis using Freesurfer software. Data analysis employed Mann-Whitney U and χ^2 tests, considering $p < 0.05$ as significant.

Results: SZH and HC groups showed no significant differences in age and gender. However, significant ($p < 0.05$) alterations in Gray Matter (GM) volume were observed in SZH patients compared to HC. In the right hemisphere, several regions exhibited volume reduction, including the Fusiform sulcus, Rostral middle frontal gyrus, isthmus cingulate, Frontal pole, Middle temporal gyrus, Lateral occipital gyrus, and Inferior Parietal gyrus. Notably, the Precentral sulcus and Postcentral gyrus demonstrated volume acceleration. Similarly, in the left hemisphere, various regions showed volume reduction while the Paracentral gyrus indicated volume acceleration, all significant ($p < 0.05$).

Conclusion: SZH patients display significant volumetric brain changes, indicating potential for future diagnostic procedures in SZH.

More Information

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Submitted: December 12, 2023
Approved: January 02, 2024
Published: January 03, 2024

How to cite this article: Fanayi M, Oghabian MA, Naghavi HR, Farrahi H. Comparative Study of Cerebral Volumetric Variations in Patients with Schizophrenia with their Unaffected First-degree Relatives, using Magnetic Resonance Imaging Technique, a Case-control Study. J Neurosci Neurol Disord. 2024; 8: 001-007.

DOI: 10.29328/journal.jnnd.1001088

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Keywords: Schizophrenia; Most prevalent positive symptom; MRI; Unaffected first-degree relatives; Volumetry; Case-control

Abbreviations: DSM: Diagnostic and Statistical Manual of Mental Disorders; HC: Healthy Control; MMSE: Mini–Mental State Examination; MRI: Magnetic Resonance Imaging; PET: Positron Emission Tomography; PHA-3: Parahippocampal Three; PANSS: Positive and Negative Syndrome Scale; VBM: Voxel-Based Morphometry; SPM: Statistical Parametric Mapping; SZH: Schizophrenia; EOS: Early-Onset Schizophrenia; STG: Superior Temporal Gyrus; IPL: Inferior Parietal Lobe; FES: First Episode Schizophrenia; ROI: Region of Interest; SAPS: Scale for The Assessment of Positive Symptoms

Introduction

Schizophrenia (SZH) is a complex and chronic mental disorder characterized by disturbances in thoughts, perceptions, emotions, and behavior [1]. The symptomatic spectrum of schizophrenia includes positive symptoms, such as hallucinations and delusions, negative symptoms involving social withdrawal and diminished emotions, and cognitive impairments affecting attention, memory, and executive functions [2]. The prevalence rate of schizophrenia is 1% [3,4].

Despite extensive research, the definitive diagnosis of SZH relies just on clinical evaluations due to the absence of specific laboratory tests [5]. However, advancements in neuroimaging techniques, particularly Magnetic Resonance Imaging (MRI), have offered insights into the structural changes within the brain associated with SZH [6]. Understanding the neurobiological basis of schizophrenia has been a focal point in psychiatric research, with neuroimaging techniques such as Magnetic Resonance Imaging (MRI) offering insights into structural brain alterations associated with the disorder [7]. Numerous studies have explored the neural underpinnings of schizophrenia, aiming to elucidate structural brain alterations associated with the disorder [8-10]. Past studies have shown cortical thinning patterns most in the temporal, medial, and orbitofrontal regions, insula, basal ganglia, and posterior cingulate [11-14]. However, the cause of brain volume reduction in schizophrenia still remains unclear [15,16].

In fact, we cannot be sure these volumetric changes are a result of the severity of the disease itself. Most of the recent studies compared SZH with a control group that had no genetic relationship with each other but If SZH is compared with healthy first-degree relatives, we can minimize the genetic, and environmental factors, and normal variations. studies comparison of SZH with unaffected relatives reported a reduction in basal ganglia, the amygdala, putamen, and the parahippocampal gyrus [17-19].

This study focuses on individuals with Schizophrenia, specifically targeting patients exhibiting the most prevalent positive symptom. The investigation aims to unravel structural cerebral variations in SZH with the HC individuals selected from the first-degree relatives using Magnetic Resonance Imaging (MRI) techniques.

Methods

Inclusion/exclusion criteria and patient selection

After the clinical interview by a psychiatrist, 15 SZH patients with the most prevalent positive symptoms were selected from Rozbeh Hospital Psychiatry Clinic (Tehran, Iran). In this era, the positive and negative symptoms were evaluated using a semi-structured PANSS scale (with 30 questions based on a 7-point Likert scale) [20]. To prevent the inclusion of people with general cognitive decline, the Mini-Mental State Examination (MMSE) as a cognitive test was used to screen the possible cognitive impairment [21]. To measure people's intelligence, the Wechsler Intelligence Scale (WIS) was also used [22]. All patients were diagnosed using the Diagnostic and Statistical Manual of Mental Disorders DSM-V criteria. Thus, the inclusion criteria were right-handed, 18 years - 60 years old, IQ score > 70, and MMSE scale > 25. Exclusion criteria were a history of brain tumors, cerebral cysts, head injury, neurosurgery, shock therapy, drug and alcohol dependence, and being claustrophobic. The samples from both sexes were synchronized in terms of gender. The HC group was selected from first-degree relatives with no history of major psychiatric and medical disorders.

MRI technique

All people participating in the research were scanned by the 3 Tesla MRI machines (Imam Khomeini Hospital Imaging Center, GE company model Discovery 750, 3 Tesla magnet power, and 64 channels). A standard brain coil was used for imaging. In this study, although T1w images were needed, the FSPGR sequence was also used (Field of view = 256 mm × 256 mm, flip angle = 12°, TE = 3248 ms, TR=8468 ms, number of slices = 180, slice thickness = 1 mm, gap = 0, and inversion time = 450 ms).

Image processing

Free Surfer software (version 5.0.0; http://surfer.nmr.harvard.edu/) was hired to perform the automatic reconstruction of the cortical surface and anatomical divisions of cerebrum including Inferior Parietal gyrus, Isthmus Cingulate gyrus, Middle/Inferior temporal gyrus, Postcentral gyrus, Precentral sulcus, Medial/Lateral orbitofrontal gyrus, Caudal/Rostral Middle Frontal sulcus, Paracentral gyrus/sulcus, Fusiform sulcus, Frontal Pole gyrus, and Lateral Occipital gyrus/sulcus. The images were analyzed based on the following steps, ordinary; Motion correction and conform, NU (Non-Uniform intensity normalization), Talairach transform computation, Intensity Normalization-1, Skull Strip, EM Register (linear volumetric registration), CA Intensity Normalization, CA Non-linear Volumetric registration, Remove neck, LTA with skull, CA Label (volumetric labeling, i.e., Aseg) and statistics, Intensity normalization-2, White matter segmentation, Edit wm with aseg, Fill, Tessellation, Smooth-1, Inflate-1, Qsphere, Automatic topology fixer, Final surfs, Smooth-2, Inflate-2, Spherical mapping, Spherical registration, contralateral hemisphere, Map average cuvature to subject, Cortical parcellation – desikan-killiari and Christophe (labeling), Cortical parcellation statistics, Cortical ribbon mask, and Cortical parcellation aping to aseg [23].

Data analysis

SPSS software (v. 26.0.0.1) was hired for statistical analysis. The case and control comparison was applied using Mann-Whitney U and χ^2 tests for age and gender, respectively. $p < 0.05$ was also applied for the level of significance.

Results

Demographic and clinical findings

The individuals were aged from 18 to 60 years and the average age for case and HC groups were 31.6 ± 3.73 and 51.00 ± 6.3 years, respectively. Also, no significant (p = 0.081) age-associated differences were detected between both groups of case and HC. In the HC group, 9 and 6 females and males were detected, besides 6 and 9 females and males were found in case individuals, respectively. Statistical analysis of gender revealed no significant differences (p = 0.08) between case and HC groups (Table 1).

Volumetric cerebral variations in left and right hemispheres

Table 2 represents the volumetric changes of the left hemisphere in SZH patients, 9 different clusters of altered GM volume were observed. 8 clusters (inferior parietal G, isthmus cingulate G, inferior temporal G, postcentral G, lateral orbitofrontal G, medial orbitofrontal G, rostral middle frontal G, caudal middle frontal G) showed decreased volume, and 1 cluster (Paracentral G&S) had accelerated volume of the GM in SZH patients in the left hemisphere compared to the HC (Figure 1A&B). Table 3 represents the volumetric changes of the right hemisphere in SZH patients, 9 clusters of altered volume were also detected. 7 clusters (Fusiform S, Rostral middle frontal G, Isthmus cingulate S, Frontal pole G, Middle temporal G, Lateral occipital G&S, and Inferior Parietal G) showed a decreased volumetric change and 2 clusters (Precentral S and Postcentral G) represented an accelerated volumetric change in GM of SZH patients than the HC (Figure 1C&D).

Discussion

In the present study, the surfaced-based method was used for structural image analysis. GM volume of the whole brain was assessed in SZH with the most prevalent positive symptoms compared with unaffected first-degree relatives. GM cortical thinning was detected in right fusiform, right inferior parietal, right lateral occipital, right middle temporal, right frontal pole, left inferior temporal, left medial orbitofrontal, left caudal middle frontal, left lateral orbitofrontal, bilateral rostral middle frontal and bilateral isthmus cingulate. Also, GM cortical thickening was found in the right precentral postcentral and left paracentral gyri. To our knowledge, there are a few studies regarding the brain structural changes in SZH patients with the most prevalent positive symptoms. In the present study, unaffected first-degree relatives were considered as control individuals to minimize the interfering effects of anatomical deficits, and genetic and environmental factors. The obtained results supported that the SZH is considered a structural deficit.

Table 1: Demographic and clinical data of case and control groups (*n* = 15 for each).

		SZH	HC	*p* - value
Age (year)		31.6 ± 3.73		0.081
Gender (female and male)		6f & 9m	9f & 6m	0.08
PANSS	Positive	13.20 ± 1.2	-	-
	Negative	18.20 ± 9.29	-	-
	General	29.00 ± 3.2	-	-
	Total	61.40 ± 15.5	-	-
MMSE		27.40 ± 2.13	-	-

PANSS: The Positive and Negative Syndrome Scale; MMSE: Mini-Mental State Examination; m: Male; f: Female; HC: Healthy Control; PZH: Schixophrenia

Table 2: Cerebral volumetric changes in the left hemisphere of SZH patients.

Cluster NO	Cluster size (mm²)	Cluster wise *p* - value	MNI coordinates (Main peak)			Main involved structure
			X	Y	Z	
1	2616.31	0.0002	-44.3	-76.6	11.3	Inferior Parietal G
2	845.26	0.0006	-4.3	-33.3	31.7	Isthmus Cingulate G
3	839.41	0.0008	-50.2	-57.2	-10.9	Inferior Temporal G
4	756.43	0.0024	-61.1	-12	32.6	Postcentral G
5	573.88	0.01415	-19.4	16.5	-19.9	Lateral Orbitofrontal G
6	567.89	0.01633	-36.8	-0.5	45.2	Caudal Middle Frontal S
7	566.46	0.01653	-35.1	34.6	14.6	Rostral Middle Frontal S
8	541.3	0.02227	-6.2	20.3	-16.1	Medial Orbitofrontal G
9	-524.55	0.02563	-3.5	-33.1	65.1	Paracentral G&S

G: Gyrus; S: Sulcus

Table 3: Cerebral volumetric changes in the right hemisphere of SZH patients.

Cluster no	Cluster size (mm²)	Cluster wise *p* - value	MNI coordinates (Main peak)			Main involved structure
			X	Y	Z	
1	6126.3	0.0002	32.6	-53.6	-6.3	Fusiform S
2	349.33	0.0004	42.6	-73.9	21.1	Inferiorparietal G
3	714.62	0.0018	40	38.6	20.8	Rostral middle frontal G
4	611.63	0.0059	12.8	-51.7	6.9	isthmus cingulate S
5	559.19	0.0109	8	63	-5.5	frontal pole G
6	479.55	0.0291	59.3	-5.4	-23.3	middle temporal G
7	1363.61	0.0002	44.1	-77.5	-12.4	lateral occipital G&S
8	289.92		63	-5.5	58.8	Postcentral G
9	-1996.62	0.0002	39.5	-6.4	51.3	Precentral S

G: Gyrus; S: Sulcus

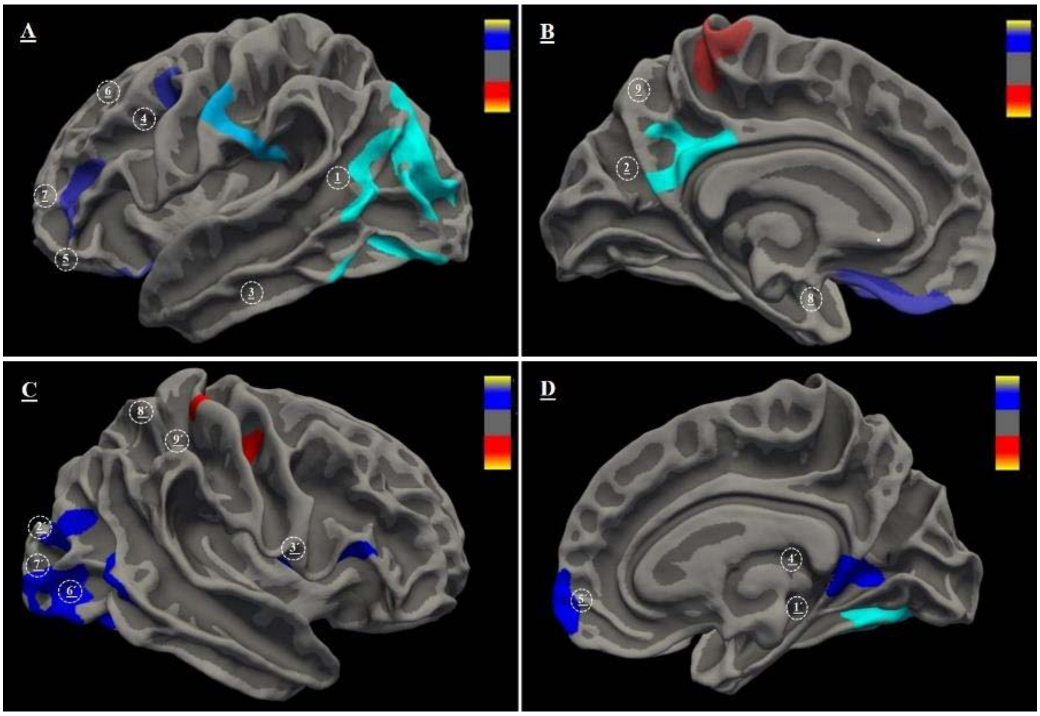

Figure 1: Volume changes in the left (A&B) and right (C&D) hemispheres of SZH patients with the most prevalent positive symptoms. The colored areas represent the changes in brain volume; blue and yellow represent decreased volume and red color showed the accelerated volume. 1-9 are clusters in the left hemisphere (A&B. 1: Inferior parietal gyrus, 2: Isthmuscingulate gyrus, 3: Inferior temporal gyrus, 4: Postcentral gyrus, 5: Lateralorbitofrontal gyrus, 6: Caudalmiddlefrontal sulcus, 7: Rostralmiddlefrontal sulcus, 8: Medial-orbitofrontal gyrus, and 9: Paracentral gyrus and sulcus) and 1´-9´ are cluster in the right hemisphere (C&D. 1´: Fusiform sulcus, 2´: Inferior Parietal gyrus, 3´: Rostral Middle Frontal sulcus, 4´: Isthmus Cingulate gyrus, 5´: Frontal Pole gyrus, 6´: Middle Temporal gyrus, 7´: Lateral Occipital gyrus and sulcus, 8´: Postcenral gyrus, and 9´: Precentral sulcus).

The human brain possesses information pertaining to both internal and external stimuli, which can be retained in both conscious and unconscious states. In addition to the aforementioned data, intricate neural networks and structures exist within the human brain that facilitate the retention and storage of said information [24]. In individuals diagnosed with schizophrenia and presenting with predominantly positive symptoms, the neural structure responsible for the retention and storage of information is disrupted. Due to the aforementioned alterations, the accurate representation of oneself and objects within memory becomes unavailable in individuals with schizophrenia who display prominent positive symptoms. The emergence of positive symptoms, such as delusions and hallucinations, appears to initiate a cascade of changes that result in the impairment of accurate self-representation and object memory in individuals with schizophrenia [25]. Delusion and hallucination are prominent clinical manifestations in individuals with schizophrenia who exhibit predominant positive symptoms [26]. Our investigation revealed a reduction in gray matter volume across various brain regions in individuals with schizophrenia who display predominant positive symptoms. The alterations in these regions appear to be associated with the emergence of the aforementioned symptoms.

Structural alterations have been identified in brain regions that are implicated in the genesis of hallucinations and delusions. Specifically, the middle temporal region is known to play a crucial role in cognitive processing, such as language and semantic memory processing, while the inferior temporal region is involved in visual perception [27,28]. The present study's results indicate that a decrease in the volume of the left inferior temporal and right middle temporal regions may serve as a potential etiological factor for the manifestation of hallucination. The lateral occipital region has been identified as a potential contributor to the onset of hallucinations, as it is involved in the process of object recognition [29,30]. Our study findings indicate a reduction in the right lateral occipital lobe among our subjects. However, a separate study reported a bilateral reduction in this region. The Inferior Parietal Lobe (IPL) is a crucial neural region that contributes to a diverse range of cognitive processes, including basic attention, language, and social cognition [31]. The supramarginal gyrus, a constituent of the inferior parietal lobe, is involved in the processing of phonological information and the regulation of emotional responses [32]. The supramarginal gyrus is responsible for receiving auditory input and the inferior parietal lobe is stimulated when processing new sounds. These regions, along with the superior temporal gyrus, are implicated in the manifestation of delusions and hallucinations. Notably, a study found a reduction in volume of the left inferior parietal lobe, while no volumetric reduction was observed in the supramarginal gyrus.

The isthmus cingulate is an integral component of the limbic system, which contributes to the regulation of memory and emotions [33]. Research has demonstrated that damage to the isthmus cingulate is linked to depressive symptoms [34]. Our investigation revealed a bilateral decrease in isthmus cingulate volume, while Wei, et al. observed a reduction in the left isthmus cingulate [33].

The frontal pole is a center for higher cognitive functions and has been demonstrated to be significantly impacted in schizophrenia [13,35-37]. In this study, we observed a reduction in the volume of the right frontal pole, which is consistent with the findings of Snelleksz, et al. [38] and Prasannakumar, et al. [36]. Additionally, a reduction in the volume of the fusiform gyrus was observed in the right hemisphere, which may account for deficits in facial recognition and memory [39]. The precentral cortex, which contains motor fibers and contributes to voluntary movements, has been shown to undergo changes in schizophrenia. In our investigation, we observed an increase in the volume of the precentral cortex, which is inconsistent with some prior studies that have reported a decrease in volume [40]. The orbitofrontal cortex is involved in reward and punishment responses and may be implicated in thought disorders. Our results indicate a reduction in the volume of the left medial and lateral orbitofrontal cortex, which aligns with the findings of Nakamura, et al. [41]. Finally, a reduction in the volume of the paracentral lobule has been observed in mental disorders, but we found an increased volume in schizophrenia patients with dominant positive symptoms, which has not been reported in previous literature.

The middle frontal gyrus is a crucial region involved in short-term memory and its volumetric changes have been linked to a decline in basic skills and social functioning, making it a valuable marker for early diagnosis of schizophrenia. In our study, we observed a reduction in cortical volume in the left rostral and caudal middle frontal gyrus and the right rostral middle frontal gyrus in patients with schizophrenia.

The postcentral gyrus contains somatosensory neurons that play a key role in object recognition, texture differentiation, and sensory-motor response This system receives information from half of the body in each hemisphere of the brain and is the primary center for touch and movement sensation. Alterations in the volume of this region in patients with schizophrenia have been linked to reduced sensory-physical sensitivity, perceptual distortion, and poor prognosis [42]. Our findings indicate a reduction in the volume of the left postcentral gyrus and an increase in the volume of this area in the right hemisphere. Previous studies have reported a bilateral decrease or right-sided decrease in this region in patients with schizophrenia [43].

It is important to acknowledge certain limitations of our study. Firstly, all patients included were receiving antipsychotic medication, making it difficult to exclude the potential influence of medication on brain morphology. Secondly, our sample size was limited to 15 schizophrenia patients with dominant positive symptoms and 15 controls, warranting further replication with larger sample sizes to validate our results. Thirdly, in this study, there is no significant difference in age between the Schizophrenia cases and the control cases; But if the sample size increases, the control group may be significantly older. These differences in age within the control group could potentially affect the volume comparison between the two groups. We emphasize the need for caution in interpreting our findings and highlight this aspect as a point for future research or considerations in subsequent studies exploring similar studies.

Conclusion

In conclusion, the present study investigated structural brain abnormalities between individuals with schizophrenia patients with dominant positive symptoms and first-degree unaffected relatives. We found GM decreases in multiple regions, including the right middle temporal, right lateral occipital, right supramarginal, right frontal pole, left inferior temporal, left inferior parietal, and bilateral isthmus cingulate, which may have important roles in the delusion and hallucination underlying schizophrenia patients with dominant positive symptoms.

Acknowledgment

The authors wish to thank Dr. Zahra Shad for their contribution to patient selection and associated procedures.

Authors' contributions

MF gathered the patients and conducted the main procedure of the survey, MAO proposed the research plan and guided the study, HRN was responsible for MRI analysis, and HF analyzed the statistics.

Funding

This paper was extracted from the MSC thesis (Thesis NO: 9811754002). Tehran University of Medical Sciences is hereby commended for providing the financial fund.

Availability of data and materials

The datasets used and analyzed for this are available from the corresponding author upon reasonable request.

Ethics approval and consent to participate

All included individuals were informed about the study objectives and entered the investigation with their personal consent. This thesis has been approved by the Ethics Committee of Tehran Medical School (IR.TUMS.MEDICINE.REC.1399.362).

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