Basic and Clinical
NEUROSCIENCE
May & June 2023, Volume 14, Number 3

Research Paper

Brain Structural Changes in Schizophrenia Patients Compared to the Control: An MRI-based Cavalieri's Method

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Citation Heidari, Z., Mahmoudzadeh-Sagheb, H., Shakiba, M., & Gorgich, EAC. (2023). Brain Structural Changes in Schizophrenia Patients Compared to the Control: An MRI-based Cavalieri's Method. *Basic and Clinical Neuroscience, 14*(3), 355-364. http://dx.doi.org/10.32598/bcn.2021.3481.1

http://dx.doi.org/10.32598/bcn.2021.3481.1

Article info:
Received: 16 Feb 2021
First Revision: 01 May 2021
Accepted: 07 Aug 2021
Available Online: 01 May 2023

Keywords:
Schizophrenia, Stereology, Magnetic resonance imaging, Quantitative changes, Cavalieri's method

ABSTRACT

Introduction: Schizophrenia is a severe psychotic brain disorder. One of the potential mechanisms underlying this disease may be volumetric changes in some brain regions. The present study aimed to employ magnetic resonance imaging (MRI) to estimate and quantitatively analyze the brain of patients with schizophrenia compared to the controls.

Methods: This case-control study was conducted on MRI scans of 20 patients with schizophrenia and 20 healthy controls in Zahedan City, Southeastern Iran. MRIs with 4 mm slice thickness and 5 mm intervals in coronal and sagittal planes were captured. Then, quantitative parameters, including volume and volume density of various brain regions, were estimated in both groups using Cavalieri's point counting method. Data analyses were performed using the Mann-Whitney U test.

Results: The findings of this investigation revealed that volumes of gray matter, hippocampus, and gray/white matter in patients with schizophrenia were significantly lower than the controls ($P<0.05$). The volumes of lateral ventricles in patients with schizophrenia (36.60 ± 4.32 mm^3) were significantly higher than the healthy individuals (30.10 ± 7.98 mm^3). However, there were no statistically significant differences between the two groups regarding the changes in the brain's total volume, cerebral hemispheres, white matter, brain stem, cerebellum, and corpus callosum ($P>0.05$).

Conclusion: Volumetric estimations on brain MRI-based stereological technique can be helpful for elucidation of structural changes, following up the treatment trends, and evaluating the therapeutic situations in schizophrenia patients. Volumetric alternations in specific brain areas might be linked to cognitive impairments and the severity of symptoms in patients with schizophrenia. Further research is needed in this regard.

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Highlights

- Volumetric changes occur in certain regions of the brain of schizophrenia patients.
- Structural changes in the brain of schizophrenia patients are associated with the severity of clinical manifestations.
- A brain MRI-based stereological technique can clarify neuropathology and assess therapeutic efficiency in patients with schizophrenia.

Plain Language Summary

Schizophrenia is a severe neuropsychiatric disorder with worldwide prevalence that disrupts a person's social life. It's characterized by progressive neuroanatomical alterations in both gray and white matter in different brain regions and associated with changes in the structural and functioning of some critical brain circuits. Several factors have been suggested to be involved in the development and progression of the disease including alternations and disconnection in myelin, genetic factors, neurodegenerative process, neuroinflammation, neurodevelopmental deficiencies, the number of dopaminergic neurons and volumetric changes in different areas of the brain. It has shown that quantitative volumetric brain measurements on magnetic resonance imaging (MRI) scans in patients with neurodegenerative disease owing to selective regional atrophy are beneficial for clinicians to ascertain disease progression and to evaluate volume alternations and response to treatment. Thus, we investigated structural changes of the brain in schizophrenia patients on MR images using accurate Cavalieri's estimation and compared to healthy controls. The findings demonstrated that some structural changes occurs in various brain areas which involved in many critical roles in normal brain's functionality and connectivity. On the other hand, these changes are associated with cognitive impairments and the severity of clinical symptoms in patients with schizophrenia. It's appears that elucidation of the different pathways of various structural abnormalities related to schizophrenia is required to recognize and determine the role of discrete pathophysiological phenomena in mental illness development and progress.

1. Introduction

Schizophrenia is a progressive, debilitating, and severe neuropsychiatric disorder that affects approximately 0.5%-1% of the population worldwide (Kim et al., 2015; Van Os & Kapur). Schizophrenia typically emerges in the adolescent years or early adulthood, between 18 and 25 years old, and it is frequently recognized as a chronic and lifelong disease (Insel, 2010). It is characterized by positive symptoms (hallucinations, delusions, and paranoia), negative symptoms (anhedonia, social withdrawal, and behavioral disorders), and cognitive dysfunction (memory impairment, inability to maintain attention, and disruption in executive functions) (Meyer, 2013; Tandon et al., 2009). Thus far, several factors have been suggested to be involved in the development and progression of the disease, such as alternations and disconnection in myelin; genetic factors; the number of dopaminergic neurons and oligodendrocytes; volumetric changes in different areas of the brain; and neurodegenerative, neuroinflammation, and neurodevelopmental deficiencies. All these factors can lead to structural and functional changes in the brain of patients with schizophrenia (Jaaro-Peled et al., 2010; Roussos & Haroutunian, 2014). Despite extensive studies and substantial advances in genetic, neurochemical, and neurobiological theories presented on schizophrenia (Insel, 2010; Jaaro-Peled et al., 2009), the exact development, progression, and underlying pathogeneses of this complex psychological disorder are unknown and challenging for most researchers and clinicians (Murray & Lewis, 1987). As mentioned above, one of the contributing factors in the pathology of schizophrenia is volumetric changes, which can lead to structural disconnection and neurophysiological alternations in the brain of patients (Tepest et al., 2013).

In numerous investigations, the stereological technique is the recommended approach for the estimation of quantitative parameters of the brain in normal aging, neurodegenerative diseases, and schizophrenia (Heidari et al., 2017b; Pakkenberg et al., 2009). These exact and unbiased findings help us to obtain a better perception of underlying mechanisms and alternations in the development and progression in different phases (acute, chronic) of the disease (Kipp et al., 2017).

Quantitative volumetric brain measurements on magnetic resonance imaging (MRI) scans in patients with neurodegenerative disease owing to selective regional atrophy are beneficial for clinicians to ascertain disease progression and to evaluate volume alternations and response to treatment (Ciumas et al., 2008; Heidari et al., 2017b). A previous study conducted by our team on brain MRI scans of methamphetamine abusers showed that volume loss was significant in some areas of the brain in drug abusers compared to controls (Heidari et al., 2017a). Another volumetric study based on Cavalieri's point counting method on brain MRI scans of patients with Parkinson disease revealed that volume reduction in some regions of the brain in these patients was significant compared to that in the controls. These studies suggested that quantitative evaluation of MRI scans might be beneficial for clinical applications and to analyze clinical manifestations in patients (Heidari et al., 2020; Heidari et al., 2017b). Therefore, the main goal of the current study is to estimate the volumetric analysis of brain MRI scans in patients with schizophrenia and compare the results with the controls.

2. Materials and Methods

Study design and subjects

In the current case-control study, we evaluated volumetric alternations on brain MRI scans of 40 subjects in two groups: Patients with schizophrenia (n=20) and gender and age-matched healthy controls (n=20). Schizophrenia was diagnosed based on the diagnostic and statistical manual of mental disorders fourth edition, the criteria of text revision (DSM-IV TR), by an expert psychiatrist. The schizophrenia group included patients (14 males, 6 females) who had a history of the disease for at least 12 months without a history of other neurological diseases such as epilepsy, Parkinson and Alzheimer disease, mental retardation, and head trauma and taking psychoactive substances. The healthy control group included those without a history of psychiatric and neurological disorders, underlying diseases, and drug abuse. In addition, alcoholics and smokers were excluded from the study. All the subjects were enrolled by the convenience sampling method from individuals referred to the psychiatric clinic of Baharan Psychiatric Hospital, Zahedan, Southeastern Iran.

MRI protocol and volumetric estimations

Stereological estimations and quantitative measurements of brain regions in both groups were done based on Cavalieri's principle. According to this principle, for unbiased estimation of the volume of an object, it must be sectioned into a series of parallel planes with a fixed distance. To avoid bias, the first section must be placed at a random situation in a constant interval of length. The serial sections acquired from the object must be transited via the entire area (Alper et al., 2006). In the present study, the method of stereological estimation was conducted in the following manner:

At first, for estimation of volumetric parameters of various areas in the participants, FLAIR (fluid-attenuated inversion recovery) successions of structural brain MRI scans taken in two diverse anatomical axes (sagittal, coronal) with 4 mm slice thickness and 5 mm intervals were prepared. The brain structural MRIs from patients with schizophrenia and controls were captured using a three-dimensional (3D) high-resolution T1-weighted MR 1.5 T scanner system (GE systems, Paris). Next, point-counting grids that contained organized points superimposed on MRI scans and points hit the desired regions of the brain were computed by Cavalieri's point-counting method as described in our previous studies (Heidari et al., 2020; Heidari et al., 2017a; Heidari et al., 2017b). (Figure 1).

Subsequently, the brain regions' quantitative estimations (volumes and volume densities) were compared between schizophrenia and control groups. All volumetric calculations were performed using Cavalieri's point-counting Equation (Equation 1), and the results were reported as cm^3. The Points counting technique demonstrated on a sagittal brain MRI using a stereological method (Equation 1):

$$1.\ v=\frac{\sum^{m}_{j=1} p\times a/p\times t}{M^2}$$

Where v is the estimated volume of any desired object, ∑P is the sum of the number of points hitting that object in all slices, a/p is the area associated with each point in the stereological grid, t is the mean distance between the captured slices, and M is the linear magnification of the image (Heidari et al., 2020; Heidari et al., 2017a; Heidari et al., 2017b).

In the next step, an estimate of the volume density (Vv) of the brain components in the reference space (total brain) was obtained using the formula Vv=P (part)/P (ref), where P (part) is the number of test points that fall in each component profile, and P (ref) is the number of points that hit the total brain (Heidari et al., 2020).

Statistical analysis

The collected data were reported as Mean±SE, and a nonparametric Mann-Whitney U test was applied to characterize volumetric differences between the two groups. SPSS software, version 21 for windows (Chicago, IL, USA) was used for all statistical analyses. The significance level was set at P<0.05.

3. Results

The Mean±SD age of patients with schizophrenia and healthy controls was 60.4±7.09 and 61.3±6.91 years, respectively. There was no significant difference between patients and healthy participants in gender. The ratio of males to females in patients with schizophrenia and healthy participants was 14 to 6.

A comparison of the results of volumetric analysis in patients with schizophrenia and controls revealed a statistically significant increase in cerebral ventricles volume and volume density, right ventricle volume and volume density, and left ventricle volume density (P<0.05). The total volume of lateral ventricles in schizophrenia patients and healthy subjects was 36.60±4.32 mm^3 and 30.10±7.98 mm^3, respectively.

On the other hand, gray matter volume, white matter/gray matter volume, and total volume and volume density of each hippocampus were significantly lower in patients with schizophrenia than in healthy participants (P<0.05).

However, there were no statistically significant changes in the brain's total volume and volume of cerebral hemispheres, white matter, brain stem, cerebellum, and corpus callosum between the two groups (P>0.05). Additional details of volumetric changes in different brain areas of each group are presented in Table 1.

4. Discussion

In the current study, a significant reduction was found in volumes of gray matter and hippocampus in patients with schizophrenia compared to that in controls. On the other hand, despite a decrease in the total volume of the brain and volume of cerebral hemispheres and white matter in patients with schizophrenia compared to those in healthy subjects, this volume reduction was not statistically significant. In addition, the volumes of lateral ventricles significantly increased in patients with schizophrenia compared to healthy participants.

The findings of Chung et al. (2017) showed a substantial increase in lateral ventricle volume in patients with schizophrenia compared to controls. They also found a significant inverse association between ventricular volume expansion and gray matter thickness in individuals with clinically high-risk psychosis. They stated that lateral ventricular system enlargement is associated with significantly steep rates of cortical reduction (Chung et al., 2017). Another study conducted by Meduri et al. using morphometrical and morphological analyses of the

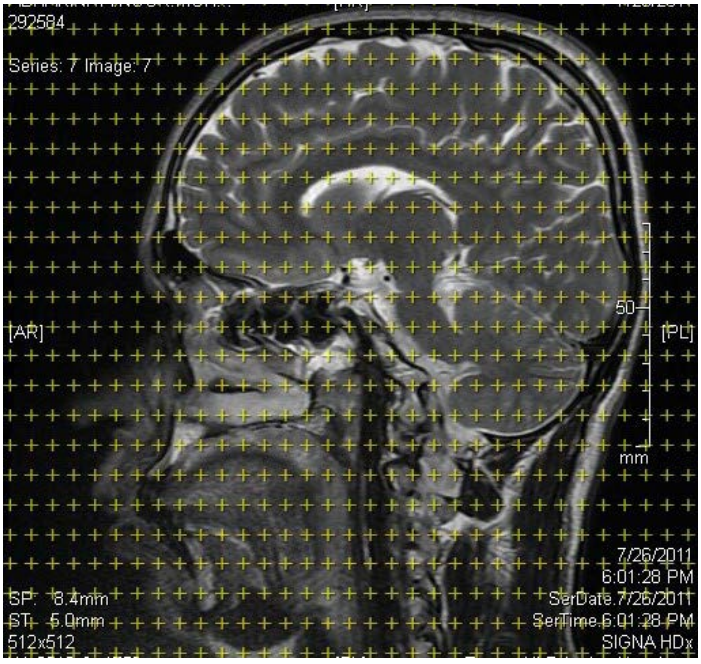

Figure 1. The points counting technique on a sagittal brain MRI using stereological method

Table 1. Stereological indices in various regions of the brain in patients with schizophrenia and the control group (n=20)

Stereological Indices	Stereological Indices	Schizophrenia	Control	Difference Percentage (%)	P
Total brain volume		1207.50±105.48	1316.10±119.57	-8.28	NS
Cerebral hemispheres	Total volume (mm^3) Volume density (%)	816.30±68.33 68.10±8.67	872.60±78.29 66.70±7.87	-6.40 2.10	NS NS
Left cerebral hemisphere	Total volume (mm^3) Volume density (%)	441.90±23.54 37.00±5.30	424.70±51.08 34.60±2.15	4.08 6.94	NS NS
Right cerebral hemisphere	Total volume (mm^3) Volume density (%)	480.40±41.22 37.50±2.44	460.30±55.15 35.10±4.49	4.34 6.84	NS NS
Cerebellum	Total volume (mm^3) Volume density (%)	134.80±14.14 11.30±1.53	133.30±17.91 10.20±1.32	0.75 10.78	NS NS
Cerebral ventricles	Total volume (mm^3) Volume density (%)	36.60±4.32 3.00±0.41	30.10±7.98 2.30±0.57	21.59 30.43	0.037* 0.003*
Left ventricle	Total volume (mm^3) Volume density (%)	18.70±2.41 4.40±0.77	15.20±5.12 3.70±1.80	23.03 18.92	NS 0.006*
Right ventricle	Total volume (mm^3) Volume density (%)	17.90±1.98 3.80±0.50	14.90±3.58 3.30±0.84	20.13 15.15	0.036* 0.005*
Brain stem	Total volume (mm^3) Volume density (%)	22.30±2.67 1.90±0.21	21.70±4.41 1.60±0.25	4.70 18.75	NS NS
Corpus callosum	Total volume (mm^3) Volume density (%)	22.90±1.04 1.90±0.17	22.70±1.06 1.70±0.14	1.32 11.70	NS 0.022*
Gray matter volume	Total volume (mm^3) Volume density (%)	321.4±35.55 26.80±4.07	395.50±38.66 30.40±4.67	-18.73 -11.84	0.0001** NS
White matter volume	Total volume (mm^3) Volume density (%)	630.9±64.65 52.60±6.90	635.60±33.67 48.60±4.41	-0.70 -8.23	NS NS
White matter, gray matter volume		0.52±0.05	0.63±0.08	-0.17	0.001*
Hippocampus	Total volume (mm^3) Volume density (%)	8.40±0.15 0.7±0.12	11.50±0.29 0.88±0.21	-26.95 -20.45	0.01* 0.034
Left hippocampus	Total volume (mm^3) Volume density (%)	4.60±0.69 1.00±0.17	5.70±0.93 1.24±0.22	-19.29 -19.35	0.004* 0.003*
Right hippocampus	Total volume (mm^3) Volume density (%)	4.50±0.59 1.02±0.15	5.90±1.40 1.39±0.56	-23.72 -26.61	0.012* 0.041*

NS: Not significant, *P<0.05, **P<0.0001.

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lateral ventricles delineated that lateral ventricle total volume, right and left ventricle total volume and volume density, and left ventricle total volume in patients with schizophrenia were significantly higher than those in the control group (Meduri et al., 2010). Morphologically, the enlargement of the ventricular system is the most significant deficit in patients with schizophrenia compared to that in the controls (Shenton et al., 2001). Therefore, the results of our research team confirmed the previous findings about lateral ventricular enlargement in patients with schizophrenia. We speculate that increased ventricular volume in patients who have schizophrenia probably is one of the fundamental findings in brain MRI of these patients, which occurs in tandem with cortical and subcortical reduction of gray matter (basal ganglia) volume (Hashimoto et al., 2018; Meduri et al., 2010). Nevertheless, a reduction in the white matter volume of adjacent lateral ventricles (Price et al., 2006) and hyperdopaminergic situations with significant neurotoxic effects (Abi-Dargham, 2014) can affect the expansion of these spaces.

The human hippocampus is one of the important brain structures with nearly 10 million glutamatergic and γ-amino butyric acid (GABA)-ergic neurons. It plays a substantial role in regulating emotion, affect, and cognitive functions. Based on neuroimaging and postmortem studies, the hippocampus is considered a key region in the early pathophysiology of schizophrenia (Konradi et al., 2011). Evidence suggests an abnormality in GABA-ergic inhibition of hippocampal pyramidal cells, impaired hippocampal interneurons, and a region-specific upregulation of GABA (A) receptor binding in patients with schizophrenia (Heidari et al., 2020). Falkai et al., in their stereological postmortem study, showed a significant reduction in glial cells and neuron numbers in subregions of the left side hippocampus in CA4 and dentate gyrus (DG), respectively, in patients with schizophrenia compared to those in healthy controls. In addition, they found that this cellular decline in the substructure of the hippocampus (CA4/DG) occurs along with the decreased volume of the total hippocampus (Falkai et al., 2016). Calvo et al. demonstrated that the total volume of right and left hippocampi in patients with schizophrenia was significantly less than in the controls. They concluded that the hippocampus volume loss in the early stages of the disease could increase patients' vulnerability to severe mental illness (Calvo et al., 2018). Reduced volume of the hippocampus subregions (CA1 and CA4/DG) occurs even in the first episode of schizophrenia and is widespread more along with disease progression. Interestingly, volume loss in different subregions of the hippocampus due to the involvement of its anterior or posterior part is associated with the severity of symptoms (Nakahara et al., 2018). Our results regarding quantitative changes and reduced hippocampus volume in patients with schizophrenia were consistent with those reported in the above-mentioned studies. Therefore, it seems that the decline in hippocampus volume occurs in the first episode of schizophrenia, and a series of metabolic and structural factors including neuronal hyperactivation in particular GABA-ergic ones, levels of different neurotransmitters, decreased numbers of neurons and oligodendrocytes plays fundamental roles in this event (Falkai et al., 2016; Lieberman et al., 2018; Nakahara et al., 2018).

Despite our findings regarding the total volume of the brain and the cerebral hemispheres that did not show any statistically significant reductions in patients with schizophrenia compared to that in the controls, many previous studies on patients with schizophrenia conducted using neuroimaging indicated that these patients had a decreased cortical brain volume compared to that in healthy individuals (Haijma et al., 2012; Pantelis et al., 2003). This issue that the reduction in cortical brain volume in patients with schizophrenia occurs due to antipsychotic drug effects or neuropathological processes is still under debate (Ho et al., 2011). Vita et al. illustrated that antipsychotic drugs affected the cortical thickness and reduced the volume of the cortical brain (Vita et al., 2015). Another study conducted by Zhang et al. showed that cortical gray matter volume in patients with schizophrenia was significantly less than that in normal subjects. In addition, they claimed and supported that the reduction in cortical volumes of the brain in patients is associated with taking more antipsychotic medicines and related to the inflammatory basis (Zhang et al., 2016). Other experimental studies reported that antipsychotic drugs could lead to neurodegeneration and negative changes in the brain volume through induction of oxidative damage and reduction in the expression of growth factors (neurotrophins). These factors play critical roles in neuronal survival and differentiation in the brain (Pillai et al., 2007). However, our results related to the total volume of the brain and cerebral hemispheres did not show any significant difference between the two groups, but a significant reduction was observed in the volume of gray matter in patients with schizophrenia compared to that in the controls. This event is feasible due to volumetric changes in subcortical structures of the brain in patients with schizophrenia. Concerning the lack of reduced brain cortical volume in our study, we agree that various factors are involved in volumetric changes, including duration of disease, levels of inflammatory mediators, and exposure to antipsychotic drugs (Hashimoto et al., 2018; Zhang et al., 2016). Furthermore, reduction in the brain volume might be exaggerated in selected areas of the brain in some patients with schizophrenia due to disease heterogeneity (Kim et al., 2017; Zhang et al., 2016).

Kim et al. demonstrated a significant reduction in the volume of white matter in patients with schizophrenia compared to that in healthy subjects, especially in the superior frontal gyrus (SFG), superior temporal gyrus (STG), and inferior temporal gyrus (ITG). In addition, they found a negative correlation between the volume of white matter in STG and disease duration. Lastly, their results suggested that any abnormality and loss of white matter volume in STG could be related to the psychopathology of schizophrenia (Kim et al., 2017). Our results showed no statistically significant reduction in total volume and volume density of white matter in patients with schizophrenia compared to those in controls. In addition, we observed no significant difference in the volumes of the corpus callosum. Still, there was a significant increase in the volume density of the corpus callosum in patients with schizophrenia compared to controls. However, the results of other studies are contrary

to changes in white matter and corpus callosum volumes in the present study (Arnone et al., 2008; de Moura et al., 2018; Del Re et al., 2016). The findings of Moura et al., which align with ours, showed no significant alternations in the corpus callosum volume in patients and healthy subjects. Their results showed that long-term exposure to antipsychotic drugs led to a greater increase in volume in some regions of the corpus callosum volume (posterior part) (de Moura et al., 2018). Amone et al., in their meta-analysis, explained that volume reduction in the corpus callosum region is more prominent in the first episode of schizophrenia, whereas patients with chronic schizophrenia showed relatively greater corpus callosum volume (Arnone et al., 2008). In addition to these results, Del Re et al. reported no substantial changes in the follow-up of patients with the first episode of schizophrenia compared to those in the controls (Del Re et al., 2016). Based on the aforementioned results, we proposed that volumetric changes in white matter and corpus callosum probably occur in specific brain areas and are associated with clinical severity symptoms. Variables affecting the volumes of white matter and corpus callosum in the brain are the duration of illness and chronic intake of antipsychotic medications. Another possible explanation for these findings (contrasting with those in different studies) could be the heterogeneity in subjects' enrolment with different disease severity and the small sample size. Nevertheless, the role of compensatory processes for the structural and volumetric changes in different regions of the brain should not be forgotten (Heidari et al., 2017a; Heidari et al., 2017b).

Some limitations we faced in this study were the small sample size, evaluation of variables such as duration of illness, number of episodes, and use of antipsychotic drugs. These limitations are suggested to be considered in designing future studies.

5. Conclusion

In conclusion, according to our findings, it seems that volumetric estimations on brain MRI-based stereological technique can be helpful for elucidation of structural changes, follow-up the treatment trends, and evaluating the therapeutic situation in schizophrenia patients. Other volumetric changes can vary in the different areas of the brain depending on the duration of the disease, antipsychotic therapy, and the inflammatory status of the patients. These changes might be linked to cognitive impairments and the severity of clinical symptoms in patients with schizophrenia. Finally, these findings can be beneficial in assessing antipsychotic treatments and dysfunctional connectivity in patients with schizophrenia. Furthermore, elucidation of the different pathways of various structural abnormalities related to schizophrenia is required to recognize and determine the role of discrete pathophysiological phenomena in mental illness development and progress. Further studies with larger sample sizes and more variables are recommended in this regard.

Ethical Considerations

Compliance with ethical guidelines

This study was approved by the Institutional Ethics Committee of the Zahedan University of Medical Sciences (Code: IR.ZAUMS.Rec.1390-2391).

Funding

This study was financially funded by Zahedan University of Medical Sciences (Grant No.: 2391).

Authors' contributions

Study design: Mansour Shakiba, Zahra Heidari and Hamidreza Mahmoudzadeh-Sagheb; Supervision: Zahra Heidari and Hamidreza Mahmoudzadeh-Sagheb; Data collection and selection of samples: Mansour Shakiba; Literature review and drafting the manuscript: Enam Alhagh Charkhat Gorgich; Data analysis: Enam Alhagh Charkhat Gorgich, Zahra Heidari and Hamidreza Mahmoudzadeh-Sagheb; Review, editing and final approval: All authors.

Conflict of interest

The authors declared no conflict of interest.

Acknowledgments

The authors appreciate all schizophrenia patients and controls who participated in the study and from Zohreh Rohani and Omid Dadras for their help in MRI data collection. We thank the Student's Scientific Association of Anatomical Sciences of Iranshahr University of Medical Sciences.

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