ORIGINAL ARTICLE

Occipital sulci patterns in patients with schizophrenia and migraine headache using magnetic resonance imaging (MRI)

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ABSTRACT

Aim To examine the presence of morphologic variations of occipital sulci patternsin patients with schizophrenia and migraine headacheregarding gender and laterality using magnetic resonance imaging (MRI).

MethodsThis study included 80 patients and brain scans were performed to analyze interhemispheric symmetry and the sulcal patterns of the occipital region of both hemispheres. Average total volumes of both hemispheres of the healthy population were used for comparison.

Results There was statistically significant difference between subjects considering gender (p=0.012)with no difference regarding age(p=0.1821). Parameters of parieto-occipital fissure (p=0.0314), body of the calcarine sulcus (p=0.0213), inferior sagittal sulcus (p=0.0443), and lateral occipital sulcus (p=0.0411) showed statistically significant difference only of left hemisphere in male patients with schizophrenia with shallowerdepth of the sulcus.

Conclusion Representation of neuroanatomical structures suggests the existence of structural neuroanatomic disorders with focal brain changes. Comparative analysis of occipital lobe and their morphologic structures (cortical dysmorphology) in patients with schizophreniausing MRI, according to genderindicates a significant cortical reduction in the left hemisphere only in the group of male patients compared to female patients and the control group.

Keywords: morphologic variations, neuropathology, neuroradiology

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Original submission:
18 March 2016;
Revised submission:
02 May 2016;
Accepted:
23 May 2016.
doi: 10.17392/855-16

Med Glas (Zenica) 2016; 13(2):

INTRODUCTION

Schizophrenia is a complex mental disorder where environmental factors interacting with the genetic susceptibility and early neurodevelopmental aberrations, precede the onset of psychotic symptoms. It remains one of the most intriguing psychiatric research topics with a worldwide prevalence of 1% leading to lifelong disability in more than 50% of the sufferers (1). This brain disorder strikes persons as they are entering the prime of their life and, in many cases, runs a recurrent and ultimately chronic course. This most devastating of mental illnesses affects the essence of what makes people human: their personality and intellect and it is considered the prototypic mental illness (2). Premorbid abnormalities in brain development might lead to anatomical and physiological alterations in widely distributed cortical and subcortical networks. The so-called „neurodevelopmental hypothesis“ suggeststhat schizophrenia is related to adverse conditions leading to abnormal brain development during the pre or postnatal period, whereas symptoms of the disease appear in early adulthood (3). It has been hypothesized that the disorder originates from brain neurodevelopmental neuropathology with symptoms and neuropsychological deficits arising from alterations in described brain regions or functional neuronal circuits(4). The neuropathological process may be related to a pre-existing neurodevelopmental loss of synaptic contacts to ongoing deficits on the synaptic and molecular level, resulting in an excessive loss of neuronal connectivity(5).

Magnetic resonance imaging (MRI) has been helpful in revealing subtle structural brain abnormalities in schizophrenia and it seems likely that the occipital lobe is involved in some aspects of the pathophysiology of disease (6).

Meta-analyses of structural MRI studies reveal brain volume deficit and it is possible that at least in some patients, an additional neurodegenerative process, beginning at the time of symptom onset, may play a role in the pathophysiology of the disease (7).Studies using MRI have shown the significance of the occipital lobe as the brain region of higher interest for understanding the schizophrenic psychosis (8-10). The search for the regions of cerebral mass responsible for generating schizophrenic symptoms lead to new insights on its functional organization.

The aim of the study was to determine the morphologicdifferences in the brain structuresof occipital region regarding gender and lateralitybetween patients with schizophrenia and patients with migraine headacheusing MRI**.**

PATIENTS AND METHODS

Patients and study design

This prospective, comparative study included 80 patients of both sexes, 21–67 years old, classified into two groups: S groupincluded 40 patients with schizophrenia (21 malesand 19 females)andM (control) group with 40 patientswith migraine headache (10 malesand 30 females). The study was conducted atthe Department of Psychiatry and Neurology, University Clinical Center Sarajevo, during the period of four years (2011-2015). Magnetic resonance imaging (MRI) scans of both the left and the right hemispheres of occipital lobe of 80 human brains were examined at the Department of Radiology,University Clinical Center Sarajevo. Coronal sections and descriptive analysis of the occipital lobe were performed according to gender. The sulci (regions) of interestof the occipital lobe through the magnetic resonance imaging volume of a single patient(control and patient with schizophrenia) wereidentified (ROI): parieto-occipital fissure (POF), temporo-occipital incisure (TO), body of the calcarine sulcus (BCS), anterior sulcus calcarinus (ACS), retrocalcarine sulcus (RCS),inferior sagittal sulcus (ISGS), superior sagittal sulcus (SSGS), transverse occipital sulcus (TOS), lateral occipital sulcus (LOS), inferior occipital sulcus (IOS), posterior collateral sulcus (PCS) 3.8, lingual sulcus (LiS) 1.7, lunate sulcus (LuS).

The Ethics Committee of the University Clinical Center Sarajevo had givenan ethical consent to perform the study. All subjectssigned a written informed consent before the enrollment.

Patients (S group) included in the study were 18 to 67 yearsoldwho were on the hospital treatment and under antipsychoticdrugs at the Department of Psychiatry, and had been diagnosed with schizophreniaaccording to ICD-10 criteria(11). Patients were included into the research on the basis of consecutive admissions taking into account that all of them were with a long psychiatric history (at least 5 years of hospital treatment)

andobtained signed information consent within clinical research.

The criteria for the exclusion referred to: the appearance of psychotic phenomenology within neurological disease, organic psychosyndrome, somatic disease, neurological disorder (head trauma, brain insult, epilepsy), information on drug or alcohol abuse,metal content in the body or the absence of signed informed consent for voluntary participation.

For the group of patients with schizophrenia, the average age was 41.50 (SD±10.44; range 22–67) years.

The control group (M group)represented patients 18 to 55 years old, based on admissionsat the Department of Neurology, diagnosed with migraine headache criteria(12), whowere tested with the test scales of assessment with the signed informed consent for voluntary participation. This group included subjects who had never suffered psychotic or severe neurological disorders (head injuries, epilepsy) or diseases, and in whose anamnesis there had beenno information on drug or alcohol abuse,with nometal content in the body and who signedinformed consent for voluntary participation.

The average age was 38.50 (SD±6.59; range 30–53) years.

The groups were equal according to age (p=0.691).

Methods

Neuroradiology method-Magnetic resonance imaging (MRI)

The MRI scans were performed on a Siemens 3T superconducting magnet system to get very strong and homogeneous field-T2TSE3D-RST-TRA(Avanto, Siemens, Erlangen, Germany). The relaxation time T2 (TR=750/TE114) with sequences of turbo spin echo (TSE) in transverse planes and layer thickness of 0.6 mm, T1 sequence (voxel resolution: 1mm×1mm×1.25mm, TI:20ms, TD:500ms, TR:9.7ms, TE:4.0ms, FLIP:10, Matrix:256×256, Rect. FOV: 7/8, Partitions:128, Time=13 min and 12 seconds)were applied. For the purpose of group analysis sulcus depth(mm), t-statistical map was generated for each hemisphere with the application of $t>2.66$ ($p<0.01$, with the rate of freedom of 61). Two statistical methods, group analysis of size and interhemispheric symmetry, were used in order to test significant differences of sulcus depth between groups.

Volumes of the sulcal patterns of the occipital region (cc) of both left and right hemispheres for each patientwere investigated to providea quantitative description of the variability of the location of a given brain structure (a sulcus). Anatomical variability of the sulci of the occipital region in standard stereotaxic space in the form of probability maps was examined. The image data were resampled onto a standard grid with cubical voxels 1 mm wide. The gray-matter voxels extending for 1 mm on either side of the banks of the sulcus were included in the set of voxels constituting the sulcus. We identified occipital sulci and marked their corresponding gray matter voxel on magnetic resonance images around POF, TO, BCS, ACS, RCS,ISGS, SSGS, TOS, LOS, IOS, PCS, LiS, and LuS.

Average total volumes(cubic centimeters, cc) of both left and right hemispheres of the healthy population for comparison were as follows: POF24.0, TO 1.1, BCS 11.2, ACS 7.5, RCS 2.7, ISGS 1.9,SSGS 1.8, TOS 7.2, LOS 5.8, IOS 1.9, PCS 3.8, LiS 1.7, and LuS 2.5 (13,14).

Statistical analysis

The research task was to define the differences betweenpatients with schizophrenia andpatients with migraine headacheaccording to demographic data (gender,age) and morphology of the brain regions using MRI of both groups.For the purposes of correlation and associative analysis multivariate analysis of variance, Pearson's correlation coefficientand Point-biserial correlation wereapplied using χ^2 test, T-test of independent samples, T-test of paired samples, Kolmogorov-Smirnov testand Levene`s test for equality of variances.

Statistically significant differences were considered $p<0.05$.

RESULTS

Demographic data

The study was conducted on a group of 80 subjects divided into two groups: patients with schizophrenia (40) and control group (40) with migraine headache.

Among 40 patients with schizophrenia 21 (52.5%) were males and 19 (47.5%) females;in the control group 10 (25.0%) patients were males and 30 (75.0%) females(p=0.012) (Table 1).

Table1. Age distribution of patients

Age (years)	No (%) of patients			
	Schizophrenia group		Control group	
	Male	Female	Male	Female
20-30	5 (23.8)	1 (5.3)	4 (0.4)	6 (0.2)
30-40	8 (38.1)	5 (26.3)	1 (0.1)	12 (0.4)
40-50	5 (23.8)	8 (42.1)	3 (0.3)	9 (0.3)
50-60	2 (9.5)	4 (21.1)	2 (0.2)	3 (0.1)
60-70	1 (4.8)	1 (5.3)	/	/
Total	21	19	10	30

Average age of patients with schizophreniawas 41.50±10.43 years, and of controls 38.50±9.48 years. The youngest subject in schizophrenia group was 22, and the oldest one 67; in the control group the youngest was 20, and the oldest 55 (Table 2) (p=0.1821).

Table 2. Morphologic structures ofoccipital lobe according to gender

Group of patients / variables	Volume (cubic centimeters)		p
	M (mean)	MS (mean square)	
Schizophrenia			
Parieto-occipital fissure(POF) left (male)	22.490	84.872	0.0314
Parieto-occipital fissure (POF) right (male)	22.404	82.595	0.0377
Control			
Parieto-occipital fissure (POF) left(male)	24.550	85.421	
Parieto-occipital fissure(POF) right (male)	23.560	85.513	
Schizophrenia			
Body of the calcarine sulcus (BCS) left (male)	9.713	33.411	0.0213
Control			
Body of the calcarine sulcus (BCS) left(male)	11.005	36.138	
Schizophrenia			
Inferior sagittal sulcus (ISGS) left (male)	1.730	1.378	0.0443
Control			
Inferior sagittal sulcus (ISGS) left (male)	1.993	2.779	
Schizophrenia			
Lateral occipital sulcus (LOS) left (male)	5.545	11.705	0.0411
Control			
Lateral occipital sulcus(LOS) left (male)	6.310	19.090	

Comparative analysis ofoccipital lobe and their morphologic structures using MRI according to gender (controls and patients)

The morphological variation of the sulci of the occipital region of the human brain was examined in both left and right hemispheres in 80 patients (controls and patients with schizophrenia) on magnetic resonance images.

Significant differences between the groups were registered onthe left hemisphere of occipital lobe with some specific regions only in male patients with schizophrenia (Figure 1, 2).

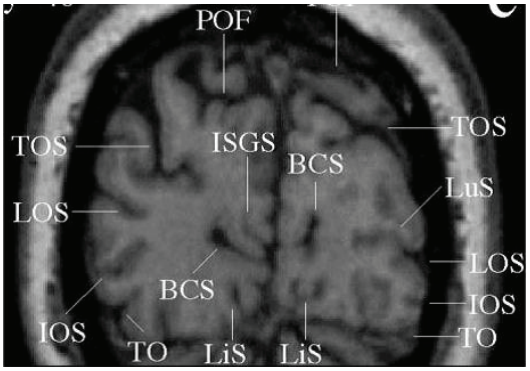

Figure 1. Coronal sections of the occipital lobe through the magnetic resonance imaging volume (controls) (Hodžić M., Institutzaradiologiju UKCS, 2013)
POF, parieto-occipital fissure, TO,temporo-occipital incisure, BCS, body of the calcarine sulcus, ISGS, inferior sagittal sulcus, TOS, transverse occipital sulcus,LOS, lateral occipital sulcus, IOS, inferior occipital sulcus, LiS, lingual sulcus, LuS, lunate sulcus

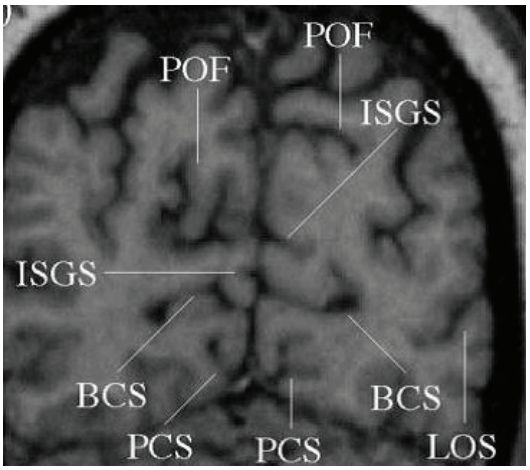

Figure 2. Coronal sections of the occipital lobe through the magnetic resonance imaging volume (patients)(Mašić R./Institutzaradiologiju UKCS, 2013)
POF, parieto-occipital fissure, BCS, body of the calcarine sulcus, ISGS, inferior sagittal sulcus, LOS, lateral occipital sulcus, PCS, posterior collateral sulcus

The appearance of the different patterns of the sulci of parieto-occipital fissure regarding gender showed statistically more significant difference on the left side (M=22.490;SD=9.073;p=0.0314) compared to the right side (M=22.403; SD=9.215;p=0.0377) only in male patients with schizophrenia (Table 2).

Patterns of body of the calcarine sulcus showed statistically significant differences in these parameters regarding gender only in male patients with schizophrenia (M=9.713; SD=4.530;p=0.0213), without differences on the right side in the same group (m=10.218; SD=5.977). (Table 2).

In parameters of inferior sagittal sulcus regarding gender statistically significant difference was noticed only in male patients with schizophrenia (m=1.730; SD=1.656;p=0.0443), without differences on the right (m=1.490; SD=0.909) (Table 2).

Statistically significant difference in parameters of lateral occipital sulcus regarding gender was noted only in male patients with schizophrenia(m=5.545; SD=4.467;p=0.0411), with no differences on the right side of these patients (M=4.640;SD=4.326) (Table 2).

In all investigated parameters of occipital sulci patterns in the control group there were no statistically significant differences (Table 2).

DISCUSSION

Schizophrenia is linked to damaged structure of the occipital cortex. Understanding any alteration of the brain among people suffering from schizophrenia, as well as the occipital lobe functions, can contribute to a better understanding of changes in the brain associated with early stages of the disease or its progression (15). Gender differences are evident in the morphology of brain structure in a healthy population, and studies point to identical differences in regions of the brain among men and women suffering from schizophrenia using MRI (16). Castle and Murray investigated these regions and concluded that evidence ofsuchdifferences exists (17). Studies conducted using MRI revealed a reduction of the coronal brain region, a small left hippocampal formation and enlargement of the lateral ventricle in men, but not in women (18). Research conducted using MRI suggests that many of the structural changes occur in sexually dimorphic areas of the brain (19).Studies of gender differences in the context of schizophrenia, indicate that although the developing the disease is roughly the same among genders, men tend to develop schizophrenia earlier, with a worse prognosis and a premorbid history(17). This is the so-called period of high risk for schizophrenia and occurs between the ages of 20 and 39(15). Men, therefore, tend to be younger than women at the onset of the disease(16).Age distribution is very important when it comes to evaluating the possibility or risk of the development of the disorder. This concerns lifetime risk and in order to evaluate it, it is necessary to consider the age distribution of the population that we are examining(17).

The lifetime risk for schizophrenia is between 0.3 and 3.7% depending on the methodology used (17).In our study, with regard to the age of patients, the minimum age in both groups was around 20, while the maximum age in the group of patients with schizophrenia was 67, and in the control group 55. Members of the group diagnosed with schizophrenia were on average 3.5 years older than those in the control group. The illness was manifested differently among the genders, with men having undergone previous psychiatric treatment and hospitalization, and also in relation to various socio-cultural factors which have an influence on early diagnosis of the disease among males (20).One hypothesis as to why schizophrenia develops later in women is the protective effect of estrogen, as it has been determined that there is a negative correlation betweenthe negative symptoms of schizophrenia and plasma concentrations of estrogen(20). The effects may be structural or functional. Structural effects are due to developmental changes in regard to earlier development of the brain in women, from the prenatal period to adolescence. Neuronal connections, lateralization of brain functions and axonal myelination are established earlier in female brains than in those of males. This slower level of development could make the male brain more vulnerable to earlier damages, resulting in structural brain abnormalities associated with the early onset of the illness and its negative symptoms(21). The hypothesis that estrogen has an antipsychotic effect, modifying the functional operation of neurotransmitters and plays a protective role against the development of psychotic symptoms explains the gender-differences in schizophrenia. Five MRI studies reported volume reduction in the occipital lobe

in schizophrenia while Davatzikos et al. reported reduced gray matter in occipital association areasin patients with schizophrenia (22).Our research conducted using MRI revealed changes in the occipital lobe, especially of the left hemisphere (shallower depth of sulcus).

In terms of gender, among a group of male patients with schizophrenia, significant differences were registered in the parieto-occipital fissure, calcarine sulcus, lower sagittal sulcus and the lateral occipital sulcus, which is consistent with a study conducted by Andreasen and associates (23,24).The results of our study are consistent with a study that compared the morphology of the cerebral cortex and its pattern of gyri and sulci depth of the occipital lobe in patients with schizophrenia, and in the area of the left hemisphere; a difference in the depth of the sulcus (shallower) was evident and was correlated with the degree of impairment of working memory and occipital lobe executive function (25).A study examining cortical dysmorphology in patients with schizophrenia revealed diffuse cortical reduction in the left hemisphere in the group of male patients, which correlates with our results (25, 26, 27). Among the group of male patients higher right occipital lobes in relation to the left, and lower left frontal lobes in relation the right were recorded and also a change in the asymmetry of the occipital lobe, but not the frontal lobe, while Luchins and his team reproduced their earlier findings of changes in the normal asymmetry of the occipital and frontal lobes in patients with schizophrenia (28,29).Descriptive statistical parameter values of the region of interest, as part of the occipital lobe, indicate significant differences in the group of male patients compared to female patients and the control group. Changes are present only on the left side of the calcarine sulcus, lower sagittal sulcus and the lateral occipital sulcus, while the areas of the temporo-occipital incisure, the posterior and anterior ends of the calcarine sulcus, transverse occipital sulcus, the lower occipital sulcus, the occipital region of the left and right hemisphere, did not exhibit statistically significant differences among the two groups.

Our findings are consistent with studies that examined the morphology of the cortical surface, and those which recorded a reduction of the gyrus index in both cerebral hemispheres of 3% -4.5%, but it was more pronounced in the area of the left side (30-33), which is consistent with the findings of five studies conducted in relation to the volume of the occipital lobes in schizophrenia (34-38).In our study a descriptive comparative analysis of morphological variations in the occipital sulcus region of both hemispheres using MRI revealed the presence of significant differences particularly in the area of the left hemisphere in the group of male patients.

The consistency of the findings reveals distinct multiple brain regions, which show changes in the gray matter of patients with chronic forms of schizophrenia (39-41).

What has become known as the “typical” pattern of anatomical asymmetry, the dominance of the left parieto-occipital region– was described in the early years of the 20th century with speculations that it is connected to the functional improvement of the cerebral hemispheres. The possibility of the development of mental diseases can be associated with a “disorder” of the normal models of brain asymmetry. Representation of neuroanatomical structures in vivo suggests the existence of structural neuroanatomic disorders, ranging from evidence of focal brain changes, primarily of gray matter and its identification, and focus on damage of the brain. Schizophrenia is a heterogeneous disorder with varying manifestations and pathophysiology. It does not have a single *sine qua non* symptom, but rather a variety of symptoms which can occur in individual patients.

FUNDING

No specific funding was received for this study.

TRANSPARENCY DECLARATION

Conflict of interest: None to declare.

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Okcipitalna regijapacijenata oboljelih od shizofrenije i migrenozne glavobolje primjenom magnetno rezonantnog prikaza (MRI)

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SAŽETAK

Cilj Istražiti prisustvo morfoloških razlika sulkusa okcipitalnog režnja pacijenata oboljelih od shizofrenije i migrenozne glavobolje u odnosu na spol i lateralnost primjenom magnetno razonantnog snimanja (MRI).

Metode Studija je uključila 80 pacijenata kod kojih je urađeno magnetno snimanje u svrhu analize interhemisferne simetrije i uzoraka sulkusa okcipitalne regije obje hemisfere svakog ispitanika. Prosječne ukupne vrijednosti volumena obje hemisfere zdrave populacije primijenjene su u komparativne svrhe.

Rezultati Statistički značajne razlike između ispitanika evidentirane su u odnosu na spol (p=0,012), bez razlika kada se posmatra dobna struktura (p=0,1821). Kada se posmatraju vrijednosti parametaraparietookipitalne fisure (p=0,0314), tijela sulkus kalkarinusa(p=0,0213), donjeg sagitalnog sulkusa(p=0,0443), lateralnog okcipitalnog sulkusa(p=0,0411), postojale su statistički značajne razlike samo u području lijeve hemisfere muških ispitanika oboljelih od shizofrenije s plićim sulkusima.

Zaključak Prikaz neuroanatomskih moždanih struktura ukazuje na prisustvo strukturalnih neuroanatomskih promjena s fokalnim moždanim promjenama. Komparativna analiza okcipitalnog režnja i njegovih morfoloških struktura (kortikalna dismorfologija) kod pacijenata oboljelih od shizofrenije u odnosu na spol primjenom MRI-a, ukazuje na značajnu kortikalnu redukciju lijeve hemisfere samo u grupi muških ispitanika komparirano sispitanicama i kontrolnom grupom.

Ključne riječi:morfološke varijacije, neuropatologija, neuroradiologija