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Morphological changes of the temporal lobe structures in schizophrenia and their link to the clinical symptoms regarding the gender difference and asymmetry

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ABSTRACT

Temporal lobe dysfunction leads to a model of the cognitive impairments in schizophrenia. The aim of this study was to evaluate changes in grey and white matter volume, cortical area and cortical thickness of the temporal lobe in schizophrenic patients and to explore the functional significance of these changes through correlation with clinical symptoms of patients as measured with the positive and negative syndrome scale. 88 control subjects and 57 chronic schizophrenics were participated in the study. Structural magnetic resonance imaging was performed and the DICOM images were evaluated using automatic brain segmentation software (BrainSuite). The volume and volume fraction of the region of interest were evaluated. The mean volume of temporal lobe was smaller in the schizophrenics (154.20±16.49 cm^3) than that of controls (174.85±17.70 cm^3), ($p \leq 0.05$). Mean volumes of the temporal grey and temporal white matter in schizophrenics (110.41±12.25 cm^3 and 43.81±4.96 cm^3) were smaller than that of controls (124.14±13.15 cm^3 and 50.71±6.29 cm^3), ($p \leq 0.05$). The mean cortical area pial in schizophrenics (425.8±40.95 cm^2) was smaller than that of control (462.30±44.42 cm^2), ($p \leq 0.05$), while no differences found between schizophrenics and controls related to the thickness of the temporal lobe ($p > 0.05$). The male patients tend to have positive correlation between the volumes and the positive symptoms. The present study suggests that patients with schizophrenia have a generalized temporal deficit. Surface area of the temporal lobe was smaller in the schizophrenics both for males and females. However, the cortex was proportionally thinner in the male schizophrenics. Positive correlations were observed between the volume and positive symptoms more in the male patients. Finally, there was no asymmetry in the volume of temporal lobe.

1. Introduction

The temporal lobe is nearly 17% of the volume and surfaces of the human cerebral cortex. The temporal cortex consists of areas involved with the auditory, olfactory, vestibular, and visual senses, and in the perception of spoken and written language (Kiernan, 2012). The temporal lobe and associated structures have been previously involved in the neuropathology of schizophrenia. The temporal lobe has believed prominently in the studies of schizophrenia, which is not surprising assumed the importance of this brain region for auditory and language processing, as those two processes are remarkably abnormal in schizophrenia.

Structural brain-imaging studies have found that reduction in the grey matter region of temporal lobe are associated with deficits in auditory sensory (Rabinowicz et al., 2000), language (DeLisi, 2001), memory (Harrison, 2004) and social cognitive processing (Green et al., 2005), which are widely documented in schizophrenia. Moreover, volume reduction of the white matter in the temporal lobe of schizophrenic patients may reflect abnormalities of some or all of the temporal systems (Sigmundsson et al., 2001; Okugawa et al., 2002). In addition, asymmetrical morphological abnormalities are particularly apparent in the temporal lobe and on the left side of the brain. (Neckelmann et al., 2006).

However, it remains unknown whether patients with schizophrenia have progressive decrease in overall temporal lobe tissue or they have localized volume reduction within temporal lobe. It is nonetheless essential to note that whole temporal lobe volume may be less informative with respect to the neuropathology of schizophrenia than volume differences in specific structures within the temporal lobe. For our knowledge this is the first study to evaluate general temporal lobe structures in schizophrenics.

This study was designed to assess the volume, thickness and surface values of the temporal lobe and structures in the patients with schizophrenia in magnetic resonance images (MRI) using automatic brain segmentation and parcellation. Asymmetry in the volume was also searched. We also explored the functional significance of any changes in the temporal lobe and its structures through correlation with clinical symptoms of patients as measured with the positive and negative syndrome Scale (PANSS).

2. Material and methods

88 control subjects (51 male, 37 female) and 57 schizophrenic patients (30 male, 27 female) were participated in the study. The study was approved by the Ethical Committee of the Gezira University/Sudan, depending on the statement of the ethical principles as developed on the World Medical Association Declaration of Helsinki (World Medical, 2013). Patients or patient's relatives and controls consented to all procedures.

2.1. Criteria of selection

Schizophrenics met ICD/10 criteria and were receiving regular antipsychotic medications were included to the study. The patients were selected from Professor Abdelaal Alidresi Psychiatric hospital, Tigani Almahi Psychiatric hospital, and private psychiatry clinics in Sudan.

Controls were Sudanese volunteers with no history of psychiatric disorders and drug medication. Control subjects were matched with patients on the basis of gender and age. Exclusion criteria for both Schizophrenics and controls include a head trauma, drug abuse and central neurological disorders.

A physician filled a descriptive questionnaire both for controls and patients, including socio-demographic data, physical data, and positive and negative syndrome scale (PANSS), which is a medical scale used for measuring symptom reduction of schizophrenic patients.

2.2. MRI acquisition

Structural neuroimaging was performed on MRI scanner (1.5 Tesla SIEMENS) in the National Ribat University/Sudan. T1-weighted images were obtained using three-dimensional acquisition by Magnetization Prepared Rapid Acquisition (MP-RA). It produces good grey/white matter contrast in a very short acquisition time. Slice distance was 1.0 mm, the field of view was 250 read, 192 mm phase, TR=1657 ms, TE=2.95 ms, bandwidth 180 Hz/pixel, flip angle 15°, ECHO spacing=7.5 ms, phase resolution=100%, slice resolution=50%, and acquisition time=5 minutes and 18 seconds. The images were in coronal section.

Analysis of MRI

The DICOM images of whole participants were analyzed blindly using a series of software: 1) Image J software; were the images re-sliced, re-oriented and converted to Analyze 7.5 image format. 2) BrainSuite software; were images in Analyze format transferred to the structural brain analysis program, and then the following stages are performed:

- The skull strip stage of the processing is controlled and adjusted manually to grantee the delineation of the brain tissue.
- Splitting hemispheres, surface and volume registration stages were done automatically (Shattuck and Leahy, 2002; Dogdas et al., 2005; Joshi et al., 2007).
- Following visual quality control, the volumes of ROIs were produced by the software (Fig. 1).

The volume of the temporal lobe, temporal grey and temporal white matter, the temporal cortical area

Table 1. Comparison of the mean of the age and BMI and the percentage of hand preference between controls and schizophrenics

		Case (%)	The mean of age (Years ±SD)	The mean of BMI (kg/m²±SD)	The percentage of hand preference	
					Right hand (%)	Left hand (%)
Male	Control	51 (58)	28 ± 5.97	24 ± 4.02¥	92.20	7.80
	Schizophrenic	30 (52.60)	30 ± 5.97	22 ± 3.49¥	93.30	6.70
Female	Control	37 (42)	29 ± 6.14	25 ± 4.83	94.60	5.40
	Schizophrenic	27 (47.40)	31 ± 6.77	24 ± 6.31	96.30	3.70
Total	Control	88 (60.70)	29 ± 6.01	25 ± 3.38*	93.20	6.80
	Schizophrenic	57 (39.30)	31 ± 6.31	23 ± 5.08*	94.70	5.30

¥*= Sig. ($p<0.05$); **BMI:** Body mass index

pial, and the temporal lobe thickness were obtained automatically in millimeters (mm), all data were collected on a master sheet designed for that purpose and volumetric data were calculate in centimeters (cm). The volume fraction/surface fraction data of the subject were calculated using the following formula (Sahin and Elfaki, 2012):

Volume/Surface Fraction = (Volume-surface of X phase in Y reference space)/(Volume-surface of Y reference space)%

The lateralization index (LI) for each subject was calculated using the following formula (Luders et al., 2004):

LI=2*(R-L)/(R+L)

LI>0 in left hemisphere or LI<0 in right hemisphere: more leftward asymmetry (left>right). While, LI<0 in left hemisphere or LI>0 in right hemisphere: more rightward asymmetry (right>left).

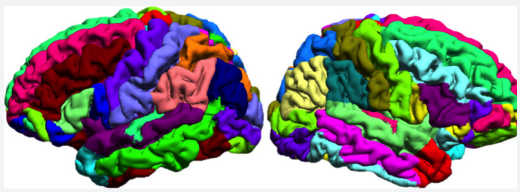

Fig. 1. An MR image of a subject after automatic structural analysis in the BrainSuite/ The ROIs are labeled and the surface is reconstructed

2.4. Statistical analysis

Statistical package for social science (SPSS version 18) was employed for all statistical analyses. Different tables and graphs were used to produce the findings. Four analyses were assumed on the measurements of the temporal lobe and its structures. Independent sample T-test was used to compare the mean volume and volume fraction of the temporal lobe, grey and white matter between controls and schizophrenics. However, Independent sample T-test, also was used to compare the mean of surface area and surface area fraction of cortical areas and temporal lobe thickness between controls and schizophrenics. Chi-square was used to compare the leftward or rightward asymmetry between groups. Degree of association between volumetric and surface area measurement and PANSS symptom subscales was tested using standard Spearman correlation test. A p value 0.05 or less was accepted as statistically significant.

3. Results

Schizophrenic patients and healthy comparison subjects were well matched for gender, age, body mass index, and handedness (Table 1). Left Handed people were excluded during the evaluation of the volumetric measurements and asymmetry of the temporal lobe and its structures.

3.1. Evaluation of volume of the hemisphere

The volumes of right, left, and total hemisphere were larger in the males than that of the females both for the control and schizophrenic groups ($p\leq0.050$). The volumes of right, left and total hemisphere were less in the schizophrenics when they are compared to the controls ($p\leq0.050$), the details of the volume data and statistical comparisons are shown in the (Table 2).

3.2. Evaluation of volume and volume fraction of the temporal lobe

Volume: In controls the mean volumes of the right, left, and total temporal lobes were larger in males than females ($p\leq0.050$). While, in schizophrenics the mean volumes of the right and total temporal lobe were larger in males than females ($p\leq0.050$), and there is no difference between male and female regard the volume of the left temporal lobe ($p>0.05$). The comparison between control and schizophrenic groups and between sexes across the groups showed significant differences in the volume of the right, left and total temporal lobes ($p\leq0.050$); the volumes of schizophrenics were less than that of the controls. The details of the volume data and statistical comparisons are shown in the (Table 2).

Volume fraction: In controls, the volume fraction of the right and total temporal lobes were larger in males (22.66±1.10% and 23.33±1.03%), respectively, than females (21.93±1.07% and 22.80±1.00%), respectively, ($p\leq0.050$), and there is no differences between male and female regard the volume fraction of the left temporal lobe ($p>0.05$). In schizophrenics, the volume fraction of the right temporal lobe was larger

Table 2. Comparison of the mean volume (cm^3±SD) of the hemispheres and temporal lobe between controls and schizophrenics

		Volume of hemisphere			Volume of temporal lobe		
		Right	Left	Total	Right	Left	Total
Male	Control	391.00Φ* ± 26.81	389.51β£ ± 26.27	780.52€Ǫ ±52.67	88.73πΘ ± 8.68	93.52δŋ ± 8.63	182.25wñ ± 16.79
	Schizophrenic	349.79Φ∞ ± 29.96	346.52βΘ ± 30.46	696.31€Ж ± 59.99	78,88πα ± 6.98	81.64δ ± 9.41	160.52wμ ± 15.04
Female	Control	361.76θ* ± 24.51	361.49Ω£ ± 25.50	723.24ΨǪ ± 49.77	79.33φΘ ± 6.75	85.59ωŋ ± 7.42	164.91εñ ± 13.69
	Schizophrenic	326.98θ∞ ± 29.33	326.69ΩΘ ± 28.14	653.68ΨЖ± 57.38	70.52φα ± 7.79	76.9ω ± 8.04	147.44εμ ± 15.49
Case	Control	378.52¥ ± 29.53	377.55ώ ± 29.31	756.07Э ± 58.55	84.72Ь ± 9.16	90.14Γ ± 9.00	174.85ø ± 17.70
	Schizophrenic	338.81¥ ± 31.55	336.98ώ ± 30.76	675.78Э ± 62.04	74.86Ь ± 8.44	79.36Γ ± 9.02	154.2ø ± 16.49

Φθ ¥ *∞ β Ω ώ £ Θ € Ψ Э Ǫ Ж π φ Ь Θ α δ ω Γ ŋ w ε ø ñ μ = Sig. (p<0.05)

in males (22.57±1.06%) than females (21.55±1.16%) (p≤0.050), and no differences found between male and female regard the volume fraction the left and total temporal lobe (p>0.05). The comparison between control and schizophrenic groups and between sexes across the groups showed no significant difference regard the volumes fraction of the right, left and total temporal lobe (P>0.05).

temporal lobe (p>0.05). The volumes of white matter of right, left and total temporal lobe were less in the schizophrenics when they are compared to the controls (p≤0.050). The details of the volume data and statistical comparisons are shown in the (Table 4).

Volume fraction: The mean volume fraction of white matter of right, left, and total temporal lobe showed no significant differences between males and females within the groups and across the groups (p>0.05).

Table 3. Comparison of volume (cm^3±SD) of grey matter of the temporal lobe between controls and schizophrenics

		Volume of grey matter of temporal lobe		
		Right	Left	Total
Male	Control	63.07Φ* ± 6.35	66.75β£ ± 6.65	129.82€Ǫ ± 12.63
	Schizophrenic	56.64Φ∞ ± 5.23	58.83βΘ ± 7.15	115.47€Ж ± 11.46
Female	Control	56.16θ* ± 4.80	60.34Ω£ ± 5.09	116.50ΨǪ ± 9.57
	Schizophrenic	50.29θ∞ ± 5.75	54.68ΩΘ ± 6.03	104.97ΨЖ ± 11.53
Case	Control	60.12¥ ± 6.66	64.02ώ ± 6.79	124.14Э ± 13.15
	Schizophrenic	53.58¥ ± 6.31	56.83ώ ± 6.89	110.41Э ± 12.55

Φ θ ¥ *∞ β Ω ώ £ Θ € Ψ Э Ǫ Ж = Sig. (p<0.05)

3.3. Evaluation of volume and volume fraction of the grey matter of the temporal lobe

Volume: The volumes of grey matter of right, left, and total temporal lobe were larger in the males than females both for the control and schizophrenic groups (p≤0.050). The volumes of grey matter of right, left and total temporal lobe were less in the schizophrenics when they are compared to the controls (p≤0.050). The details of the volume data and statistical comparisons are shown in the (Table 3).

Volume fraction: The mean volume fraction of the grey matter of right, left, and total of temporal lobe showed no significant differences between males and females within the groups and across the groups (P>0.05).

3.4. Evaluation of volume and volume fraction of the white matter of the temporal lobe

Volume: In control group the mean volumes of white matter of right, left, and total temporal lobe were larger in the males than that of females (p≤0.050). While, in schizophrenics group the white matter volume of the right temporal lobe was significant larger in males (p≤0.050), and no differences between male and female regard the white matter volume of the left and total

3.5. Evaluation of the surface and surface fraction of the cortical area pial of the temporal lobe

Surface area: The cortical area pial of right, left, and total temporal lobe was larger in the males than that of the females both for the control and schizophrenic groups (p≤0.050). The cortical area pial of right, left and total temporal lobe was less in the schizophrenics when they are compared to the controls (p≤0.050). The details of the surface area data and statistical comparisons are shown in the (Table 5).

Surface area fraction: In controls group the surface fraction of cortical area pial of the right temporal lobe was larger in males (22.24±1.27%) than females (21.68±1.13%) (p≤0.050), and no differences found between male and female regard the surface fraction of cortical area pial of the left and total temporal lobe (p>0.05). While, In schizophrenics group the surface fraction of cortical area pial of the right and total temporal lobe were larger in males (22.42±1.12% and 22.97±1.09%), respectively, than females (21.24±1.35% and 22.14±1.23%), respectively, (p≤0.050), and no differences between male and female regard the surface fraction of cortical area pial of the left temporal lobe (P>0.05). The comparison between controls and schizophrenics groups and between sexes across the

Table 4. Comparison of volume (cm^3±SD) of white matter the temporal lobe between controls and schizophrenics

		Volume of grey matter of temporal lobe		
		Right	**Left**	**Total**
Male	Control	25.66Φ* ± 3.16	26.77β£ ± 3.06	52.43€Ϙ ± 6.02
	Schizophrenic	22.24Φ∞ ± 2.57	22.81β ± 2.91	45.05€ ± 4.94
Female	Control	23.17θ* ± 2.90	25.24Ω£ ± 3.30	48.41ΨϘ ± 5.97
	Schizophrenic	20.23θ∞ ± 2.46	22.23Ω ± 2.53	42.47Ψ ± 4.71
Case	Control	24.60¥ ± 3.28	26.12ώ ± 3.23	50.71Ɔ ± 6.29
	Schizophrenic	21.27¥ ± 2.69	22.53ώ ± 2.72	43.81Ɔ ± 4.96

Φ θ ¥ *∞ β Ω ώ £ Θ € Ψ Ϙ = Sig. (p<0.05)

groups showed no significant difference in the surface fraction of cortical area pial of the right, left and total temporal lobes (p>0.05).

3.6. Evaluation of the thickness and thickness fraction of the temporal lobe

Thickness: The mean thickness of right, left, and total temporal lobe showed no significant differences between males and females within the groups and across the groups (p>0.05). Thickness fraction: In controls group the mean thickness fraction of right, left, and total temporal lobe showed no significant differences between the males and females (p>0.05). Controversially, in schizophrenics group the mean thickness fraction of right, left, and total temporal lobe showed significant differences between males and females (p≤0.050). The comparison between control and schizophrenic groups showed significant differences in the mean thickness fraction of right, left, and total temporal lobe (p≤0.050), same as, in the comparison between schizophrenic males and control males (p<0.050), while, there is no differences between schizophrenic females and control females (p>0.05). The details of the surface area and surface area fraction data and statistical comparisons are shown in the (Table 6).

3.7. Association between volumetric measurements and PANSS

The volume of temporal lobe, volumes of grey and white matter, cortical areas and thickness of the temporal lobe in schizophrenics were correlate positively with the most positive symptoms (Delusions, Hallucinatory behavior, Excitement, Suspiciousness/persecution and Hostility) (p<0.050), and correlate negatively with one negative symptoms (Passive/apathetic social withdrawal), (p<0.050). r values are given in (Table 7, 8).

Table 6. Comparison of the thickness (cm^2±SD) of the temporal lobe between controls and schizophrenics

		Mean thickness of the temporal lobe		
		Right	**Left**	**Total**
Male	Control	4.19 ± 0.18	4.28 ± 0.19	4.23 ± 0.17
	Schizophrenic	4.16 ± 0.21	4.19 ± 0.21	4.17 ± 0.19
Female	Control	4.19 ± 0.22	4.22 ± 0.22	4.20 ± 0.22
	Schizophrenic	4.20 ± 0.22	4.24 ± 0.21	4.22 ± 0.19
Case	Control	4.19 ± 0.20	4.25 ± 0.21	4.22 ± 0.19
	Schizophrenic	4.18 ± 0.21	4.21 ± 0.21	4.20 ± 0.19

3.8. Asymmetry of the hemisphere and temporal lobe

We evaluated relative right/left volume difference, according to the present data; there is no asymmetry difference in right/left hemisphere between control males and schizophrenic males (p>0.05). The findings showed that the right hemisphere were larger than the left hemisphere in healthy control males and in schizophrenic males (p≤0.05), while, in control females the left hemisphere were larger than the right and no differences between the two hemispheres in the schizophrenic females. There is no asymmetry difference in right/left temporal lobe between controls and schizophrenics (p>0.05). The findings showed that the left temporal lobe were larger than the right temporal lobe in healthy control and in schizophrenic patients (p≤0.05).

Table 5. Comparison of the cortical area pial (cm^2±SD) of the temporal lobe between controls and schizophrenics

		Cortical area pial of the temporal lobe		
		Right	**Left**	**Total**
Male	Control	233.33Φ* ± 22.08	246.99β£ ± 21.82	480.32€Ϙ ± 42.13
	Schizophrenic	216.39Φ∞ ± 16.99	227.24βΘ ± 19.34	443.63€Ж ± 32.38
Female	Control	210.28θ* ± 17.96	227.83Ω£ ± 18.64	438.11ΨϘ ± 35.34
	Schizophrenic	194.45θ∞ ± 20.53	212.18ΩΘ ± 21.47	406.62ΨЖ ± 41.04
Case	Control	223.49¥ ± 23.32	238.81ώ ± 22.52	462.30Ɔ ± 44.42
	Schizophrenic	205.82¥ ± 21.64	219.99ώ ± 21.58	425.81Ɔ ± 40.95

Φ θ ¥*∞ β Ω ώ £ Θ € Ψ Ɔ Ϙ Ж π δ w = Sig. (p<0.05)

Table 7. Correlation test (*P*-value) and (r) between the volumes of temporal lobe, grey and white matter of temporal lobe and the positive and negative symptoms of schizophrenics

		P1 Delusions	P3 Hallucinatory behavior	P4 Excitement	P6 Suspiciousness/ persecution	N4 Passive/apathetic social withdrawal
Volume of right temporal lobe (cm^3)	Male	0.003 (0.526)		0.012 (0.455)	0.003 (0.518)	
	Female		0.005 (0.502)			
	Total					0.005 (-.369)
Volume of left temporal lobe (cm^3)	Male					
	Female		0.006 (0.487)			
	Total					
Volume of total temporal lobes (cm^3)	Male			0.029 (0.399)		
	Female		0.002 (0.533)		0.048 (0.385)	
	Total					
Volume of GM of right temporal lobe (cm^3)		0.038 (0.380)		0.033 (0.390)	0.041 (0.375)	
	Male				0.041 (0.396)	
	Female		0.005 (0.503)			
	Total					0.024 (-.298)
Volume of GM of Left temporal lobe (cm^3)				0.041 (0.375)		
	Male					
	Female		0.002 (0.534)			
	Total					
Volume of GM of total temporal lobes (cm^3)				0.029 (0.398)		
	Male					
	Female		0.002 (0.543)		0.046 (0.387)	
	Total					
Volume of WM of right temporal lobe (cm^3)		0.000 (0.610)		0.028 (0.402)	0.001 (0.568)	
	Male					
	Female					
	Total					0.003 (-.390)
Volume of WM of left temporal lobe (cm^3)						
	Male	0.011 (0.455)			0.020 (0.421)	
	Female					
	Total	0.018 (0.312)			0.050 (0.261)	
Volume of WM of total temporal lobes (cm^3)			0.024 (0.410)		0.011 (0.459)	
	Male	0.004 (0.506)				
	Female					
	Total	0.039 (0.274)				

4. Discussion

4.1. Cerebral hemisphere and temporal lobe findings:

The present findings regarding the hemisphere are that the schizophrenic patients had reduced right hemisphere (11.72%), left hemisphere (12.04%), and total hemisphere (11.88%) volumes when they are compared to the controls. Alterations of the left hemisphere in schizophrenia are found more consistently than that of the right. The current findings support our previous study in schizophrenic's brain, as we founded that the patients have reduced total cerebral volume (Elfaki et al., 2013). And we are in agreement with the Shenton, who founded that, the left hemisphere less dense than the right in twins with schizophrenia, while the reverse was true for the healthy co-twins and control subjects. These results suggest that left hemisphere abnormality is environmentally acquired, rather than a genetic trait (Shenton et al., 2001).

The findings of this study regarding the temporal lobe are that the schizophrenic patients had reduced right temporal lobe (13.46%), left temporal lobe (13.77%), and total temporal lobes (13.62%) volumes when they are compared to the controls. In the literature, significant reduction of temporal lobe volume has been a common finding in both post-mortem (Highley et al., 1999), and in vivo brain imaging studies of schizophrenia (Unlu et al., 2014).

However, some studies found that absence of volume reduction of the overall temporal lobe tissue (Havermans et al., 1999), while the other studies reported localized volume reduction in hippocampus (Pantelis et al., 2003), amygdala (Montoya et al., 2005), superior temporal gyrus (Takahashi et al., 2010), and in Heschl's gyrus (Modinos et al., 2013). In addition to, temporal horn enlargement (Rossi et al., 1990) that associated with localized volume reduction in medial temporal lobe structures surrounding the temporal horn, suggesting replacement of brain tissue by cerebrospinal fluid (CSF). So there is a great deal of evidence shows that the reduction of temporal lobe parts in schizophrenic patients.

The present results tend to suggest that patients with schizophrenia have a generalized temporal deficit as confirmed when the total volume of temporal lobe was analysed. The present findings of reductions

Table 8. Correlation test (*P*-value) and (r) between the cortical areas and thickness of temporal lobe and the positive and negative symptoms of schizophrenics

	P1 Delusions	P3 Hallucinatory behavior	P4 Excitement	P6 Suspiciousness /persecution	P7 Hostility	N4 Passive/ apathetic social withdrawal
Right temporal cortical_area_pial (cm^2)	0.004 (0.506)	0.023 (0.415)	0.007 (0.481)	0.006 (0.490)		0.003 (-.386)
Male						
Female						
Total						
Left temporal cortical_area_pial (cm^2)		0.006 (0.493)				
Male						
Female						
Total						
Total temporal cortical_area_pial (cm^2)		0.005 (0.496)				0.014 (-.323)
Male						
Female						
Total						
Right temporal mean_thickness (mm)						
Male						
Female						
Total						
Left temporal mean_thickness (mm)			0.005 (0.527)		0.003 (0.552)	
Male		0.043 (0.269)	0.001 (0.420)	0.005 (0.527)	0.001 (0.433)	
Female						
Total						
Total temporal mean_thickness (mm)			0.040 (0.398)		0.002 (0.559)	
Male			0.023 (0.300)		0.003 (0.392)	
Female						
Total						

converge mostly with: 1) The review of Shenton, which reported of 51 MRI studies evaluating the volume of whole temporal lobe, 31 (61%) report smaller temporal lobe volume, while 20 (39%) report negative findings (Shenton et al., 2001). 2) The meta-analysis of Vita, which demonstrated that progressive cortical gray matter changes in schizophrenia occur with regional and temporal specificity (Vita et al., 2012).

However, neuroimaging studies have considerable variability in the results of schizophrenia. A number of factors may contribute to this variability, including differences in analysis methods: For example; some studies trusted a small number of thicker slices to estimate overall temporal lobe volume (Aso et al., 2001), while other studies trusted a large number of thin slices to estimate overall temporal lobe volume, thus allowing for more accurate volume estimations (Rimol et al., 2010). Other methodological differences between studies include: variability in the disorder itself, and also due to variations in sampling selection and biases concerning both patient and control samples. Compared with manual segmentation, automated techniques used in the current study increase the reliability/reproducibility. Precision of measurement is also excellent as judged by agreement with the literature (Morey et al., 2010).

In the present results there was a significant reduction in temporal lobe volume in the male patients more than in the male comparison control, same as when we compare the female patients with the female comparison control. These demonstrate that abnormal volumes of the temporal lobe were mostly evident in the patients with schizophrenia in comparison with the healthy control. The results of the current study suggest that gender does not employ a major influence on the volume of the temporal lobe.

4.2. Grey and white matter findings:

The finding of this study is showed localized diminished grey matter (GM) and white matter (WM) volume of the temporal lobe in general comparison between schizophrenics and controls and in comparison regarding the sex; there was a significant reduction in GM and WM volume of temporal lobe volume in the male patients more than in the male comparison control, same as when we compare the female patients with the female comparison control. These suggest that there may be distinctive neuropathological processes that lead to altered temporal lobe volume in patients with schizophrenia.

The present findings are in agreement with those of previous studies reporting progressive loss of temporal GM (Vita et al., 2012) and temporal WM alterations (Najjar and Pearlman, 2015). Okugawa suggested that in schizophrenics the volume of WM in the whole brain appears to be reduced, among the different brains regions, GM reduction was significant only in the temporal region (Okugawa et al., 2002).

It should be noted that our schizophrenic sample mostly included treated patients with chronic illness.

We were interested to understand the followings: when grey matter abnormalities occur in schizophrenia, is grey matter abnormalities in schizophrenia affect different brain areas and structures, is grey matter abnormalities in schizophrenia are a progressive changes, is there is evidence that the grey matter abnormalities in schizophrenia related to antipsychotic treatment.

The cohort study of Andreasen (2011) showed that reductions in brain tissue volume in patients with first-episode schizophrenia were maximum during the first interscan interval, when patients had significantly greater reductions than healthy volunteers in nearly all grey matter measurements (Andreasen et al., 2011). The meta-analysis of Vita (2012) demonstrates that progressive cortical grey matter changes in schizophrenia occur with regional and temporal specificity, and also found that time and type of antipsychotic treatment seem to counteract partially to grey matter loss, but are not able to arrest it. (Vita et al., 2012).

On the other hand, there were two hypotheses suggested WM volume reduction in schizophrenics; (1) The "Functional disconnection hypothesis" as previous studies have recognized that schizophrenia is characterized by structural disruption of a network connected cortical regions, which suggests a relationship between these deficits WM and both clinical and cognitive features of schizophrenia (Cao et al., 2013). (2) The "Anatomical disconnection hypothesis", as imaging, post-mortem and genetic studies demonstrated myelination abnormalities in WM (Sigmundsson et al., 2001; Flynn et al., 2003; Chavarria-Siles et al., 2015).

Our findings reflect the findings reported in patients with treated chronic illnesses, thus it is not clear whether WM disturbance headed at onset of the illness or appeared afterward as a result of illness course or antipsychotic treatment. However, length of illness or antipsychotic period administration did not significantly affect apparent diffusion coefficient (ADC) values of water molecules, particularly in WM (Andreone et al., 2007), suggesting that cortical WM abnormalities may not be related to chronic illness or medication. This theory suggests that at least part of the disease process (neuroanatomical changes) occurs early in life.

Moreover, temporal lobes are involved in several functions including; auditory perception, memory, speech, emotional response, and visual perception, and are likely to have a key role in abnormalities in schizophrenia. Therefore, our findings suggest that temporal GM and WM disruption may play a crucial role in dysfunction of auditory, language processing, memory and in cognitive deficits of patients with schizophrenia.

4.3. Cortical area pial and temporal lobe thickness findings:

However, volume is the product of thickness and surface area, a reduction in cortical volume may reflect reduced thickness, reduced area, or both. The ability to study these two cortical characteristics separately may enhance the opportunity to reveal more specific abnormalities and find out the relationships between cortical changes and neuropathology of schizophrenia. The automated surface reconstruction and parcellation method used in the current study allowed us to evaluate these two cortical characteristics separately.

In the current study, the cortical area pial of the temporal lobe was less in schizophrenics group than that of controls group, and also less when we compare between the male and female across the groups. In addition, the present findings showed that the mean thickness fraction of the temporal lobe were thinner in schizophrenics more than controls and in schizophrenic males more than control males, while, there is no differences between schizophrenic females and control females.

Recent surface-based methodology allowed distinction between cortical thinning and reduction in cortical area, and revealed that cortical area reduction is the most important factor in volume decrease in schizophrenia, while, cortical thinning was less prominent. (Rimol et al., 2012).

Our findings in cortical area reduction are consistent with report of Gutiérrez-Galve, that shown reduction in cortical volume, predominantly in temporal regions, due to smaller cortical area and area reductions were closely related to cognitive performance (Gutierrez-Galve et al., 2010).

Recent neuroimaging studies in cortical thickness in schizophrenics have certainly shown thinning in cortical mass are closer to our own, particularly in parts of the temporal lobes (Yang et al., 2010) and frontal (Williams et al., 2013). Changes in specific cortical areas may influence specific symptoms, as represented by association between temporal cortex thinning and hallucinations (Oertel-Knochel et al., 2013).

4.4. Association between volumetric measurements and PANSS

There have been many findings of correlation between temporal lobe structures reduction and symptom profile, the latter of which is the focus of the present study. We stayed interested in the distinction between positive and negative symptoms and whether temporal lobe structural abnormalities are specific to persons whose symptoms are predominantly positive or whether they reflect a more general abnormality of schizophrenia with persons whose symptoms are predominantly negative.

The present findings showed that the volume of temporal lobe, volumes of grey and white matter, cortical area and thickness of the temporal lobe in schizophrenics have significant positive correlation with the most positive symptoms (Delusions, Hallucinatory behavior, Excitement, Suspiciousness/persecution and Hostility), and significant negative correlation with one negative symptoms (Passive/apathetic social withdrawal).

This study was designed to assess the abnormalities of temporal lobe and its structures in schizophrenics. The current findings indicate that our patients tend to have correlation with positive symptoms more than that of the negative symptoms. It is reported that the positive symptoms were found to be related to the medial temporal cortex, amygdala, and hippocampus region. Negative symptoms were found to be related to the ventrolateral prefrontal cortex and ventral striatum (Jung et al., 2010).

Generalized deficit of temporal lobe and localized reduced GM, WM, and cortical areas of the temporal lobe, and temporal thinning which are reported in the present study are leading to the development of a psychotic illness. Loss of volume in the temporal lobe also affects the limbic system, located deep in the brain and containing the hypothalamus, amygdala and hippocampus, those structures are responsible for emotions and memory and their abnormalities are associated with the delusions, hallucinations and disordered thinking which are common among our chronic schizophrenics.

In the current study male patients tend to have significant positive correlation between the volume of the temporal lobe and its structures and the positive symptoms more than female patients. Recent studies have started to consider gender differences in schizophrenia in a challenge to clarify the heterogeneity of the disorder. Several studies have found gender differences; Riecher-Rössler found that negative symptoms were more severe in males (Riecher-Rossler and Hafner, 2000). However, most of the studies found no differences in symptoms (Hayashi et al., 2002).

Silva in his recent review, about the contribution of sex hormones to gender differences in schizophrenia mentioned that female patients with schizophrenia tend to have a more benign course and better outcomes than males, males may experience greater impact from possible neurodevelopmental risk factors for schizophrenia, such as prenatal/neonatal genotypic or environmental insults, or abnormal synaptic pruning in the brain during adolescence, resulting in earlier onset of illness, more brain abnormalities and chronicity, and poorer neurocognitive and psychosocial functioning (da Silva and Ravindran, 2015).

To explain gender differences in schizophrenia; estrogen may employ a protective effect in female patients, as estrogen is believed to support earlier maturation of the female brain during significant neurodevelopmental periods, thus reducing exposure to brain insults that might increase risk of schizophrenia, and also to contribute to earlier cognitive and social maturation of females, leading to better cognitive and psychosocial function in female patients (da Silva and Ravindran, 2015).

In addition, it was recorded that progesterone improvement of dopamine release also sometimes occurs indirectly through potentiation of estrogen primed effects on dopamine receptors, suggesting that progesterone may enhance the benefits of estrogen in schizophrenia and may support its helpfulness in treatment (Zheng, 2009); somehow this may explain the presence of severity symptoms in our male treated chronic patients.

Finally, there is no evidence of specific gender differences in the disorder. Overall, gender differences have been found in a number of variables. Additional studies in gender differences with more cases could deliver valuable material for improving our care treatment of the patients.

4.5. Asymmetry of the hemisphere and temporal lobe

Evaluating cerebral asymmetry in patients with schizophrenia is actually supportive in understanding the etiology of the disorder. A number of magnetic resonance imaging studies have found an absence or presence of asymmetry in patients with schizophrenia. However, the current findings regarding the cerebral hemisphere showed that there is no asymmetry difference in right/left hemisphere between control males and schizophrenic males.

In the line of our team findings, the study of Takao, showed no significant differences in either gray-matter volume asymmetry or white-matter fractional anisotropy asymmetry between schizophrenia patients and normal subjects (Takao et al., 2010). To our knowledge, the study of Taka, is the first study combining voxel-based morphometry and diffusion tensor imaging to assess the effects of diagnosis on gray- and white-matter asymmetry in patients with schizophrenia. Evaluation of gray and white matter is essential because disruption of neural circuits has been hypothesized as a mechanism of schizophrenia, and both gray and white matter are involved in schizophrenia.

Regarding the temporal lobe, there is no asymmetry difference in right/left temporal lobe between controls and schizophrenics. Current concepts of temporal lobe asymmetry and symptomatology of schizophrenia reflect an underlying disorganization of the cognitive systems in the temporal lobe areas rather than the whole temporal lobe. Reduced temporal lobe areas, with the left generally more frequent than right. Neckelmann

has confirmed abnormality in the speech areas in the left temporal lobe in patients with schizophrenia, with reduced grey matter density and volume on the left side compared to the right side (Neckelmann et al., 2006). The recent meta-analysis of 17 studies done by Williams, showed that reduction in grey matter volume and density in the left superior temporal gyrus in patients with schizophrenia is the most consistently reported brain structural abnormality (Williams, 2008), more than 80% of the analyzed studies reported the same abnormality (Hugdahl et al., 2009).

In the present study, we evaluated the relations between the structure and function in the schizophrenics using automatic brain parcellation technique on a large population. Our findings revealed that, the volumes of hemispheres were less in schizophrenics than that of the controls. Generalized volume decreases of temporal lobe and localized diminished in the grey and white matters were observed in the schizophrenics. The surface area of the temporal lobe was smaller in the schizophrenics and cortical thickness was thinner in the male patients. Male patients tend to have significant positive correlation between the volume of the temporal lobe and its structures and the positive symptoms more than female patients. Finally, there is no asymmetry in right/left temporal lobe between controls and schizophrenics.

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