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Full Length Research Paper

Morphometric analyses of Substantia Nigra Pars Compacta, temporal lobes and lateral ventricles in Schizophrenia Disease: MRI Study

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Schizophrenia is a serious mental disorder that affects several brain functions. MRI technology has enabled studies of brain anatomy in patients with schizophrenia aimed at understanding more about the substantia nigra pars compacta, lateral ventricles temporal lobes in schizophrenia disease. We prospectively examined 18 patients with schizophrenia (M: F=14:4, mean age: 44.77 years) and 50 healthy controls. Using a 1.5T MRI unit, we obtained oblique T_1-weighted axial images. We measured the length and width for the substantia nigra (SN), lateral ventricles and temporal lobes as well as identified signal intensity which was compared between patients and healthy controls using unpaired *t*-tests. Results showed that the signal intensity in schizophrenic patients differ from normal healthy subjects. The measured values of (SN) and Lateral ventricles in patients were significantly greater than those in healthy controls at $p<0.01$. Furthermore, no difference in temporal lobes between schizophrenia patients and controls were observed. The research shows that schizophrenia has neuro- anatomical correlation that can be seen by studying MR images.

Keywords: Morphometric analyses, Nigra Pars Compacta, temporal lobes, lateral ventricles, Schizophrenia, MRI

INTRODUCTION

Schizophrenia is a clinically complex disease (Tanskanen Päivikki, 2010) it usually begins to affect individuals during their adolescence or early adulthood. Currently, diagnoses of psychiatric disorders are made on the basis of clinical manifestations and associated psycho-social disturbances (American Psychiatric Association, 1994; World Health Organization, 1993). However, there is an evidence for diagnostic instability in psychotic patients at an early stage of illness (Haahr et al., 2008; Salvatore et al., 2009). Although an accurate diagnosis is required for appropriate treatment for patients.

Positron emission tomography (PET) studies in patients with schizophrenia have indicated increased baseline occupancy of D2 receptors by dopamine (Abi-Dargham et al., 2000). However, PET is not widely available, and its use is limited because of its high production costs and the short half-life of ^{11}C radiopharmaceuticals. Neuro imaging studies have shown structural brain differences in patients with schizophrenia (Johnstone et al., 1976; Wright et al., 2000; Nelson et al., 1998; Lawrie SM and

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Abukmeil, 1998).

Previous structural magnetic resonance imaging (MRI) studies have demonstrated gray matter reductions of fronto-temporo limbic brain regions in schizophrenia patients compared with those of healthy subjects (Ellison-Wright et al., 2008). There has been variability in results of schizophrenia MRI studies. Many factors may contribute to this variability, including differences in analysis methods, variability in the disorder itself, as well as variations in sampling selection concerning both patient and control samples (Smith and Iacono, 1986; Honea et al., 2005).

Dopamine dysfunction plays an important role in the pathogenesis of schizophrenia (Heinz and Schlagenhauf, 2010). The dopamine hypothesis suggests that excessive dopamine release results in symptoms of schizophrenia. Dopamine is mainly distributed within neurons of the substantia nigra (SN) (Sasaki et al., 2006) Neuromelanin has a T_1-shortening effect, which was a similar characteristic of the cutaneous melanin. Magnetic resonance imaging (MRI) is very sensitive to tissue T_1 relaxation and is able to depict tissue containing neuromelanin in (SN) (Sasaki et al., 2008). There are many previous reports which showed the signal decrease in Parkinson's disease using neuromelanin MRI (Sasaki et al., 2006; Kashihara et al., 2011; Schwarz et al., 2011) but there are only two reports using this technique for schizophrenia (Shibata et al., 2008; Sasaki et al., 2010).

In this study, we intend to classify schizophrenia patients and healthy subjects using analysis with MRI-based measures of substantia nigra,temporal lobes and ventricles dimensions. On the basis of previous studies, we hypothesized that:- (a) ventricles, substantia nigra length and width changes would be seen in schizophrenia patients compared with controls, (b) these MRI measures would differentiate schizophrenia patients from healthy subjects with good precision.

MATERIALS AND METHODS

T_1 ,T_2 and FLAIR-weighted MR studies of the substantia nigra were obtained for Schizophrenia disease patients, and for control subjects who were examined at the Military hospital, Khartoum-Sudan during the period from July 2012 up to July 2014. The study protocol was approved by Research Ethical Committee -College of Medical Radiological Science-Sudan University of Science and Technology. The diagnosis of Schizophrenia disease was based on clinical criteria. Patients with abnormal MR findings as abnormal high signal intensity on T_2 weighted images were excluded from the study. The control group consisted of 50 subjects 37(74%) males and 13(26%) females, 30 to 86 years old (mean age, 49.04±11.51 years) without neurologic insufficiency or abnormal findings on T_1 or T_2 weighted brain MR images. The group with Schizophrenia disease included 18 patients, 14(77.8%) were males and 4(22.2%) were females, (mean age, 44.8 years) with a mean duration of disease of 7.8 years (range, 2 to13 years).

The study was obtained Using a 1.5-T superconductive system (SIGNA HDE; GE medical systems, and Philips medical system 1.5 T. Coil: - HD 8 channels (neurovascular array).For T_2 weighted sequences; images were obtained using:-TR: 5200 ms TE: 90.2ms FOV: 25x22 cm slice thickness: 5.0 mm spacing: 1.0 mm. For T_1-weighted sequence; images were obtained using:-TR: 600ms TE: 20 ms FOV:-25x22cm, slice thickness: 5mm spacing: 1.0mm. For FLAIR TR: 9000ms TE: 80, TI: 1700–2500 ms and ETL: 16.

Measurement of the Substantia Nigra

Axial images of the brain, which included the mammillary body and red nucleus, were obtained in all control subjects and patients. At this plane where the mid- brain appeared, the substantia nigra becomes visible as crescent in shape, so we measured the width of the substantia nigra axis and then the length at the same view , the measurements were taken in (mm).

Measurement of the lateral ventricle and temporal lobes

Axial images of the brain, which included the lateral ventricle,basal ganglia,caudate nucleus ,lentiform nucleus putamen, globus pallidus and thalamus, were obtained in all control subjects and patients. At this plane we measured the width of the lateral ventricles and temporal lobes of brain and then the length at the same view, the measurements were taken in (mm).Frontal horn of lateral ventricle (at level of foramen of Monro) considered as the transverse (width for right and left ventricle) and from anterior horn to posterior horn for the length of lateral ventricle

Statistical Analysis

The relations between duration, width and length of the right and left substantia nigra, lateral ventricles were tested in the diseased group using Excel programme, because the substantia nigra and ventricles were expected to be changed with disease duration. Statistical tests were performed by using the Statistical Package for the Social Sciences, Version 16.0 (SPSS, Chicago, Illinois) Statistical comparisons of the width and length of the right and left substantia nigra, lateral ventricles and temporal lobe of brain between the control and Schizophrenia disease groups, were based on results of an unpaired Student's *t*-test. *P*- Values less than 0.005 were considered to indicate a significant difference.

Table 1. Distribution of the patient according to (Residence)

Residence	Frequency	Percentages%
Khartoum (Capital)	9	50
Western Sudan	4	22
Central Sudan (blue Nile)	3	17
North Sudan	2	11
Total	18	100%

Table 2. Distribution of the patients according to race

Race	Frequency	Percentages %
Gali	1	5.5
Nuba	4	22
Shaigi	3	16.5
Hmag	2	12
Hlfawi	1	5.5
Foor	1	5.5
Barno	1	5.5
Rbatab	1	5.5
Mali	1	5.5
Hamar	1	5.5
Flati	1	5.5
Msairi	1	5.5
Total	18	100

Table 3. Mean And Standard Deviation (SD) Minimum And Maximum Values Of The Age, Right And Left Nigra Length And Width Measured For The Control Group.

	Age/years	RT Nigra (Width) (mm)	RT Nigra (Length) (mm)	LT Nigra (Width) (mm)	LT Nigra (Length) (mm)
N	50	50	50	50	50
Mean	49.04 ±11.51	3.88 ±0.314	11.65 ±0.650	3.51 ±0.324	11.44 ±0.623
Minimum	30.00	3.02	10.21	3.00	10.18
Maximum	86.00	4.27	12.82	4.16	12.93

RESULTS

The Following tables and figures represent the data obtained from 18 Sudanese patients. All the 18 patients were clinically diagnosed as (Schizophrenia) with different symptoms; 16(89%) with Delusion, 18(100%) with Hallucination and 6 of 18 constituting (33%) criticize other different symptoms. The patients used drugs as: Haloperidol 5 (27%), Olanzapine 4 (22%), Clopixol 9(50%) and Floxixol 2(11%).Nigra signal intensity was found to be Iso signal intensity in T_1,Dark in both T_2 and diffusion and bright in inversion recovery techniques, while temporal lobes seems to be gray in T_1,T_2 and bright in Diffusion technique. Ventricles are dark in T_1, and diffusion with bright signal inT_2

Table 4. Mean And Standard Deviation (SD) Minimum And Maximum Values Of The Age, Right And Left Nigra Length And Width Measured For The Schizophrenia Disease Group.

	Age	RT Nigra (Width) (mm)	RT Nigra (Length) (mm)	LT Nigra (Width) (mm)	LT Nigra (Length) (mm)
Valid	18	18	18	18	18
Mean	44.77 ±7.78	4.10 ±0.14	11.96 ±0.30	3.91 ±0.27	11.87 ±0.25
Minimum	29.00	3.73	11.26	3.35	11.27
Maximum	55.00	4.26	12.34	4.22	12.16

Table 5. Mean and Standard Deviation (SD) Minimum and Maximum Values Of The Right And Left Temporal Lobe Length And Width Measured For The Control Group

	RT Temporal Lobe (Width) (mm)	RT Temporal lobe (Length) (mm)	LT Temporal lobe (Width) (mm)	LT Temporal lobe (Length) (mm)
Valid	50	50	50	50
Mean	40.49±4.43	78.99±5.01	40.90±3.18	77.45±5.33
Minimum	30.39	68.68	32.16	65.74
Maximum	46.47	86.56	45.80	86.11

Table 6. Mean And Standard Deviation (SD) Minimum And Maximum Values Of The Right And Left Temporal Lobe Length And Width Measured For The Schizophrenia Group

	RT Temporal lobe (Width) (mm)	RT Temporal lobe (Length) (mm)	LT Temporal lobe (Width) (mm)	LT Temporal lobe (Length) (mm)
Valid	18	18	18	18
Mean	40.35±3.003	78.98±3.29	40.72±3.01	77.84±3.8
Minimum	34.18	75.44	34.43	74.30
Maximum	45.85	84.62	45.80	85.70

Table 7. Mean And Standard Deviation (SD) Minimum And Maximum Values Of The Right And Left Lateral Ventricles Length And Width Measured For The Control Group

	RT Lateral ventricle width (mm)	RT Lateral ventricle Length (mm)	LT Lateral ventricle width (mm)	LT Lateral ventricle Length (mm)
Valid	50	50	50	50
Mean	11.79 ±2.197	68.21 ±4.38	11.38 ±1.95	66.57 ±8.70
Minimum	6.58	55.11	6.58	11.14
Maximum	16.74	73.90	16.42	73.65

Table 8. Mean And Standard Deviation (SD) Minimum And Maximum Values Of The Right And Left Lateral Ventricles Length And Width Measured For The Schizophrenia Group

	RT Lateral ventricle width (mm)	RT Lateral ventricle Length (mm)	LT Lateral ventricle width (mm)	LT Lateral ventricle Length (mm)
Valid	18	18	18	18
Mean	11.85 ±1.257	68.15 ±3.09	12.29 ±1.40	67.63 ±2.93
Minimum	10.02	57.70	10.44	57.23
Maximum	14.06	71.10	15.14	70.00

Table 9. Multiple Comparison Of The Right And Left Nigra Length And Width between control and Schizophrenia Group

Multiple Comparisons							
Dependent Variable	Group (1)	Group (2)	Mean Difference	Std. Error	Sig.	95% Confidence Interval Lower Bound	Upper Bound
RT Nigra Width	Control	Schizophrenia	-.21962-*	.0848	0.011	-.3874-	-.0519-
RT Nigra Length	Control	Schizophrenia	-.30140-*	.1303	0.022	-.5590-	-.0438-
LT Nigra Width	Control	Schizophrenia	-.40033-*	.0852	0.000	-.5688-	-.2318-
LT Nigra Length	Control	Schizophrenia	-.43296-*	.1278	0.001	-.6856-	-.1803-

*. The mean difference is significant at the 0.05 level.

Table 10. Multiple Comparison Of The Right And Left Temporal lobes Length And Width between control and Schizophrenia Group

Multiple Comparisons							
Dependent Variable	Group (1)	Group (2)	Mean Difference	Std. Error	Sig.	95% Confidence Interval Lower Bound	Upper Bound
RT Temporal lobe (Width)	Control	Schizophrenia	-.14538-	.9984	.884	-2.1186-	1.8278
RT Temporal lobe (Length)	Control	Schizophrenia	.01329	1.206	.991	-2.3712-	2.3978
LT Temporal lobe (Width)	Control	Schizophrenia	.18133	.8249	.826	-1.4490-	1.8117
RT Temporal lobe (Length)	Control	Schizophrenia	-.39002-	1.267	.759	-2.8946-	2.1145

*. The mean difference is significant at the 0.05 level.

Table 11. Multiple Comparison Of The Right And Left Lateral Ventricles Length And Width between control and Schizophrenia Group

Multiple Comparisons							
Dependent Variable	Group (1)	Group (2)	Mean Difference	Std. Error	Sig.	95% Confidence Interval Lower Bound	Upper Bound
RT Lateral ventricle (width)	Control	Schizophrenia	1.10770*	.1551	.000	.8010	1.4144
RT Lateral ventricle (length)	Control	Schizophrenia	-.42636-	.4141	.305	-1.2449-	.3922
Lt Lateral ventricle (width)	Control	Schizophrenia	1.01710*	.1643	.000	.6923	1.3419
Lt Lateral ventricle (Length)	Control	Schizophrenia	-.35220-	.4251	.409	-1.1925-	.4881

*. The mean difference is significant at the 0.05 level.

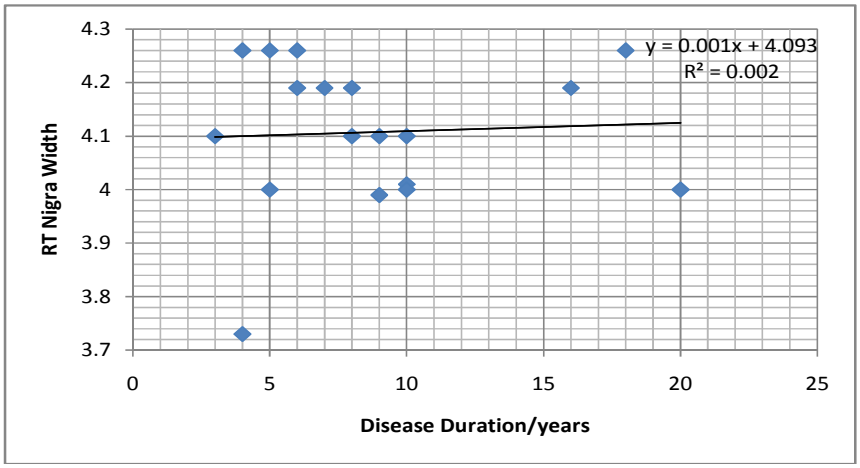

Figure 1. A scatter plot diagramme between disease duration and Right Nigra Width in Schizophrenia Group,R^2=0.002

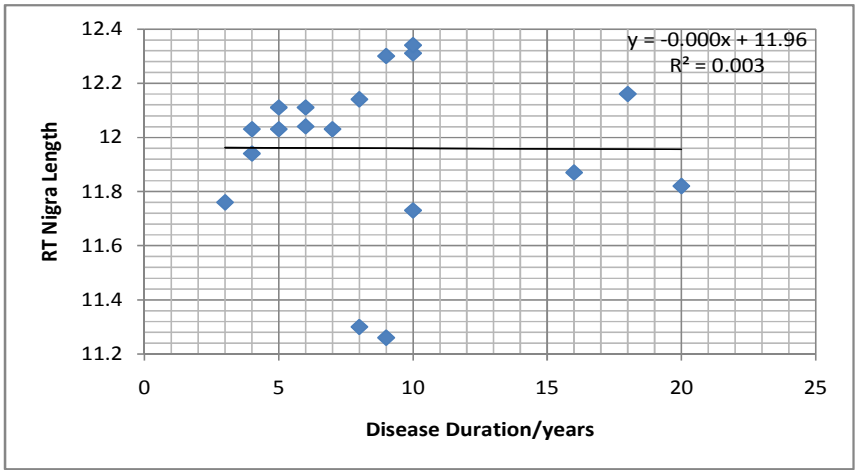

Figure 2. A scatter plot diagramme between disease duration and Right Nigra Length in Schizophrenia Group,R^2=0.003

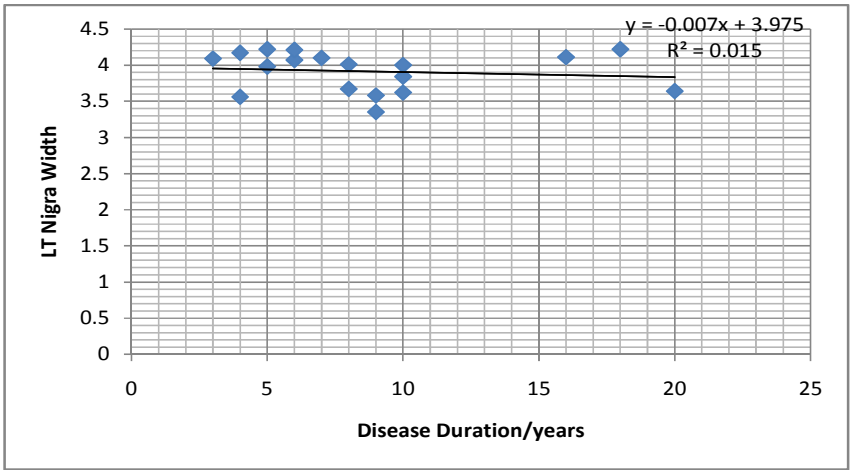

Figure 3. A scatter plot diagramme between disease duration and Left Nigra Width in Schizophrenia Group,R^2=0.015

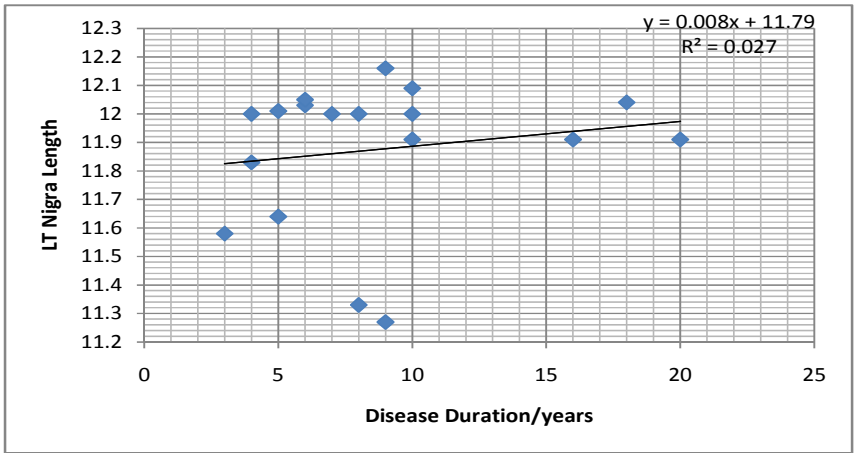

Figure 4. A scatter plot diagramme between disease duration and Left Nigra Length in Schizophrenia Group,R^2=0.27

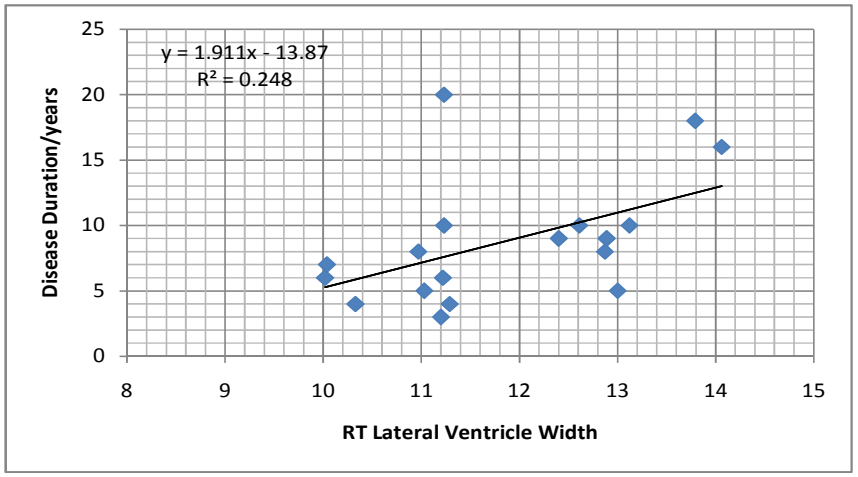

Figure 5. A scatter plot diagramme between disease duration and Right Lateral ventricle Width in Schizophrenia Group,R^2=0.248

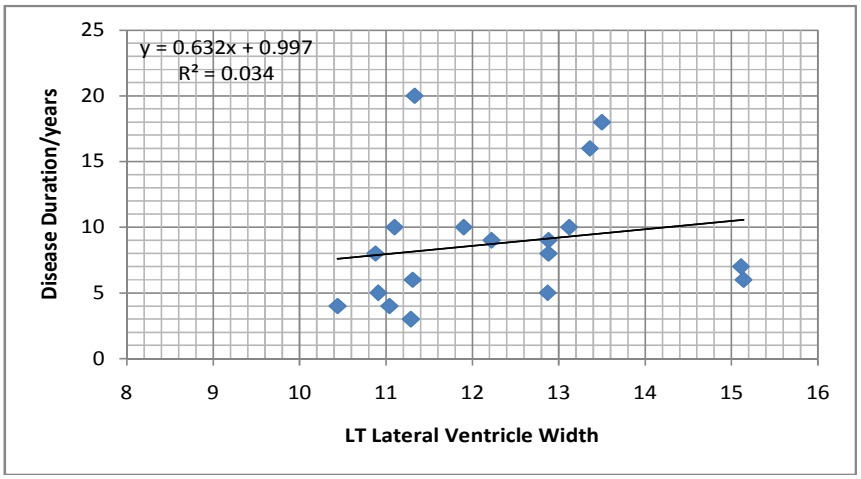

Figure 6. A scatter plot diagramme between disease duration and Left Lateral ventricle Width in Schizophrenia Group,R^2=0.034

DISCUSSION

The dopamine hypothesis suggests that excessive dopamine release results in the symptoms of schizophrenia. The purpose of this study is to elucidate the characteristics of substentia nigra, temporal lobes and lateral ventricle in patients affected with schizophrenia with mean duration of disease of 7.8 years (range: 2 to13 years)using magnetic resonance imaging (MRI) and compared the findings with healthy control subjects. The present study provides the largest set of MRI findings in patients with schizophrenia. The patients' characteristics including their residence and race distribution were presented in tables (1 and 2).

Our results demonstrate SN signal intensity changes of patients with schizophrenia and this supports the dopamine hypothesis for schizophrenia, Howers et al (Howes et al., 2013) reported the same results using a post-mortem study, which revealed that tyrosine hydroxylase staining scores were significantly greater in the schizophrenia group at substantia nigra compared to in healthy controls. It has been reported that T_1-weighted MRI with 3T can indicate T_1-shortening tissues containing neuromelanin at SN (Sasaki et al., 2008; Sasaki et al., 2006). We are aware of only two previous reports on neuromelanin imaging in patients with schizophrenia. Previous studies (Sasaki et al., 2010; Sasaki et al., 2006; Shibata et al., 2008) described signal changes in the SN among patients with schizophrenia. These previous reports indicate the signal changes in the SN in patients with schizophrenia is higher than that in controls, and our study showed also signal intensity changes but we believe that this evaluation was done subjectively by the radiologist. These results may be not accurately evaluated or generalized due to the small sample size and large variations as well as the subjectivity of the evaluation. We performed a similar comparison in our study by measuring the length and width of SN. The mean measured values was significantly higher in patients with schizophrenia than in healthy controls, Tables (3 and 4) and table (9). It is reported that neuromelanin levels in the SN can increase with disease (Zucca et al., 2006). Regarding that issue we reveal our results to that the deposited melanin in the SN reflects the measured values to be varied, and the difference between patients and healthy controls was found to be more prominent.

Our results showed that the patient group had smaller temporal lobes than healthy subjects but the differences were not significant Tables (5, 6 and 10). In another study ; subtle reductions on the order of 10–15% have been reported in the overall size of the temporal lobe (Dauphinais et al., 1990), in temporal lobe gray matter (Suddath et al., 1989), and in specific mesial (Shenton et al., 1992; Suddath et al., 1990; Bogerts et al., 1990) and lateral (Shenton et al., 1992) temporal lobe structures in patients with schizophrenia.

According to our results, lateral ventricles were enlarged in patients as compared with healthy subjects Tables (7 and 8) .The difference between the healthy and diseased patients was found to be significant table (11). Similar results were originated and it should be pointed out that patients with schizophrenia might reflect progressive ventricular enlargement, possibly related to the excitotoxic effect of repeated psychotic episodes, or might reflect an early onset non progressive developmental process (Degreef et al., 1992; Shenton et al., 2001). We also justify and referred our findings to this causes.

Regarding the duration of the diseases our study revealed that the duration of illness affected the nigra dimensions. However ventriculomegaly and reduction of the temporal lobe dimensions appear to have linear relations as illness duration increases these findings were illustrated in the figures (1-6), but adverse results were mentioned by the study done by Marsh et al (Marsh et al., 1994); this observation suggests a neuro-pathological condition. Temporal lobe abnormalities on MRI have been linked to a greater degree of auditory hallucinations (Barta et al., 1990), thought disorder (Shenton et al., 1992), and negative symptoms (Degreef et al., 1992). Our patients complain of the schizophrenia symptoms as 16(89%) with Delusion and 18(100%) with Hallucination and 6(33%) patients with other different symptoms. but our study didn't correlate the temporal lobe changes with neither the patients symptoms nor the treatment used.

There are several limitations to our study: as we didn't consider the treatment type and duration .The use of a sample including patients with a long-term exposure to drug treatment, might also limit the generalizability of the findings. Our results showed that the number of participants in this study was not enough and further study is needed .Thirdly, we used 1.5 T magnetic fields and our acquisition time is shorter than that used in previous studies (Sasaki et al., 2008; Sasaki et al., 2006) and this short acquisition might make lower signal to noise ratio and large signal variability. Future studies are needed to complement the present findings by investigating, in both patient groups and in healthy subjects, different segments of the lateral ventricles, and different subregions within the cingulate gyri, the hippocampi, and the temporal lobes

In conclusion, this finding indicates the presence of an excessive level of dopamine products in the SN of these patients. Therefore, imaging using these measurements has the potential to be useful for accurate diagnosis of schizophrenia without subjectivity and to serve as a substitute marker for medication.

REFERENCES

Abi-Dargham A, Rodenhiser J, Printz D, Zea-Ponce Y, Gil R, et al (2000). Increased baseline occupancy of D2 receptors by dopamine in schizophrenia. Proc. Natl. Acad. Sci. U S A 97: 8104–8109

American Psychiatric Association (1994). Diagnostic and statistical manual of mental disorders, 4th ed. (DSM-IV). Washington DC: APA.

Barta PE, Pearlson GD, Powers RE, et al (1990). Auditory hallucinations and smaller superior temporal gyral volume in schizophrenia. *Am. J. Psychiatry.* 147:1457–1462

Bogerts B, Ashtari M, Degreef G, et al (1990). Reduced temporal limbic structure volumes on magnetic resonance images in first episode schizophrenia. *Psychiatry Res. Neuroimaging.* 35:1–13

Dauphinais ID, DeLisi LE, Crow TJ, et al (1990). Reduction in temporal lobe size in siblings with schizophrenia: a magneti resonance imaging study. *Psychiatry Res. Neuroimaging. 35:137–47*

Degreef G, Ashtari M, Bogerts B, et al (1992). Volumes of ventricular system subdivisions measured from magnetic resonance images in first-episode schizophrenic patients. Arch. Gen. Psychiatry. 49:531–537.

Degreef G, Ashtari M, Bogerts B, et al (1992). Volumes of ventricular system subdivisions measured from magnetic resonance images in first-episode schizophrenic patients. *Arch. Gen. Psychiatry.* 49:531–537

Ellison-Wright I, Glahn DC, Laird AR, Thelen SM, Bullmore E (2008). The anatomy of first-episode and chronic schizophrenia: An anatomical likelihood estimation meta-analysis. Am. J. Psychiatry. 165(8): 1015–1023

Haahr U, Friis S, Larsen TK, Melle I, Johannessen JO, et al (2008). First-episode psychosis: Diagnostic stability over one and two years. Psychopathol. 41(5): 322–329.

Heinz A, Schlagenhauf F (2010). Dopaminergic dysfunction in schizophrenia: salience attribution revisited. Schizophr Bull 36: 472–485

Honea R, Crow TJ, Passingham D, Mackay CE (2005). Regional deficits in brain volume inschizophrenia: a meta-analysis of voxel-based morphometry studies. Am. J. Psychiatry. 162(12): 2233–2245.

Howes OD, Williams M, Ibrahim K, Leung G, Egerton A, et al (2013). Midbrain dopamine function in schizophrenia and depression: a post-mortem and positron emission tomographic imaging study. Brain. 136: 3242–3251

Johnstone EC, Crow TJ, Frith CD, Husband J, Kreel L (1976). Cerebral ventricular size andcognitive impairment in chronic schizophrenia. Lancet 2(7992): 942–926.

Kashihara K, Shinya T, Higaki F (2011) Neuromelanin magnetic resonance imaging of nigral volume loss in patients with Parkinson's disease. J. Clin. Neurosci. 18: 1093–1096

Lawrie SM, Abukmeil SS (1998). Brain abnormality in schizophrenia. A systematic and quantitative review of volumetric magnetic resonance imaging studies. Br. J. Psychiatry. 172(2): 110–120.

Marsh L, Suddath RL, Higgins N, Weinberger DR (1994). Medial temporal lobe structures in schizophrenia: relationship of size to duration of illness. *Schizophr. Res.* 11: 225–238

Nelson MD, Saykin AJ, Flashman LA, Riordan HJ (1998). Hippocampal volume reductionin schizophrenia as assessed by magnetic resonance imaging. Arch. Gen. Psychiatry. 55(5): 433–440.

Salvatore P, Baldessarini RJ, Tohen M, Khalsa HM, Sanchez-Toledo JP, et al (2009). McLean-harvard international first-episode project: Two-year stability of DSM-IV diagnoses in 500 first-episode psychotic disorder patients. J. Clin. Psychiatry 70(4): 458–466.

Sasaki M, Shibata E, Ohtsuka K, Endoh J, Kudo K, et al (2010). Visual discrimination among patients with depression and schizophrenia and healthy individuals using semiquantitative color-coded fast spin-echo T1-weighted magnetic resonance imaging. Neuroradiol. 52: 83–89

Sasaki M, Shibata E, Tohyama K, Kudo K, Endoh J, et al (2008). Monoamine neurons in the human brain stem: anatomy, magnetic resonance imaging findings, and clinical implications. Neuroreport. 19: 1649–1654

Sasaki M, Shibata E, Tohyama K, Takahashi J, Otsuka K, et al (2006). Neuromelanin magnetic resonance imaging of locus ceruleus and substantia nigra in Parkinson's disease. Neuroreport. 17: 1215–1218

Sasaki M, Shibata E, Tohyama K, Takahashi J, Otsuka K, et al (2006). Neuromelanin magnetic resonance imaging of locus ceruleus and substantia nigra in Parkinson's disease. Neuroreport. 17: 1215–1218

Schwarz ST, Rittman T, Gontu V, Morgan PS, Bajaj N, et al (2011). T1-weighted MRI shows stage-dependent substantia nigra signal loss in Parkinson's disease. Mov. Disord. 26: 1633–1638

Shenton ME, Dickey CC, Frumin M, McCarley RW (2001). A review of MRI findings in schizophrenia. Schizophr Res. 49:1–52

Shenton ME, Kikinis R, Jolesz FA, et al (1992). Abnormalities of the left temporal lobe and thought disorder in schizophrenia. *New Engl. J. Med.* 327:604–612

Shibata E, Sasaki M, Tohyama K, Otsuka K, Endoh J, et al (2008). Use of neuromelanin-sensitive MRI to distinguish schizophrenic and depressive patients and healthy individuals based on signal alterations in the substantia nigra and locus ceruleus. Biol. Psychiatry. 64: 401–406

Shibata E, Sasaki M, Tohyama K, Otsuka K, Endoh J, et al (2008) Use of neuromelanin-sensitive MRI to distinguish schizophrenic and depressive patients and healthy individuals based on signal alterations in the substantia nigra and locus ceruleus. Biol Psychiatry 64: 401–406

Smith GN, Iacono WG (1986). Lateral ventricular size in schizophrenia and choice of controlgroup. Lancet 1(8495): 1450.

Suddath RL, Casanova MF, Goldberg TE, et al (1989). Temporal lobe pathology in schizophrenia: a quantitative magnetic resonance imaging study. *Am. J. Psychiatry*. 146:464–472

Suddath RL, Christison GW, Torrey EF, et al (1990). Anatomical abnormalities in the brains of monozygotic twins discordant for schizophrenia. *New Engl. J. Med*. 322:789– 794

Tanskanen Päivikki (*2010).* Brain MRI in subjects with schizophrenia and in adults born prematurely. The Northern Finland 1966 Birth Cohort Study *Acta Univ. Oul. D 1070, 2010* Oulu, Finland

World Health Organization (1993). The ICD-10 classification of mental and behavioral disorders: Diagnostic criteria for research. Geneva, Switzerland.

Wright IC, Rabe-Hesketh S, Woodruff PW, David AS, Murray RM, Bullmore ET (2000). Meta-analysis of regional brain volumes in schizophrenia. Am. J. Psychiatry 157(1):16-25.

Zucca FA, Bellei C, Giannelli S, Terreni MR, Gallorini M, et al (2006). Neuromelanin and iron in human locus coeruleus and substantia nigra during aging: consequences for neuronal vulnerability. J. Neural. Transm. 113: 757–767