# Volumetric Brain MRI Changes in Schizophrenic Patients

RASHA EL-SHAFEY, M.D.*; AHMED MUBARAK, M.D.**; ADEL BADAWY, M.D.** and
RANIA MESHREF, M.Sc.**

*The Departments of Radiodiagnosis* and Neuropsychiatry**, Tanta University Hospital, Tanta, Egypt*

## Abstract

*Background:* The core symptoms of schizphrenia is associated with changes in volumes of specific regions of the brain.

*Aim of Study:* Is to correlate between Prefrontal Cortex (PFC), Hippocampus, (HC) and Cerebellum (CRM) volumes and schizophrenic core symptoms (cognitive, negative and positive).

*Methods:* The study included twenty schizophrenic patients and 20 matched healthy individuals as control group. DSM-IV-TR was used for diagnosis of Schizophrenia while Positive and Negative Syndrome Scale (PANSS) for symptoms assessment. 3D Slicer version 4.2.2 software was used for regional volumetric measurements. Both patients and control were assessed by [Wechsler Memory Scale (WMS), Trail Making test (TM) and Folstein Mini Mental State Examination (MMSE] cognitive tests.

*Results:* Significant decrease of volumes of HC [right, $p$=0.042,], vermis [$p$=0.02], right, $p$=0.25], PFC [left $p$=0.009, right $p$=0.006], and CRM [left $p$=0.041. The scores of WMS sub tests ($p<0.005$), MMSE ($p$=0.001) and two stages TM delay time ($p<0.01$) revealed significant reduction in patients than control. PANSS negative symptoms score revealed negative correlation with vermis ($p<0.001$) and right CRM lobe volume ($p<0.001$), while positive correlation between PANSS positive symptoms score and cerebellar vermis ($p$=0.007) and negative with both HC volumes ($p$=0.01).

*Conclusion:* Hippocampus, prefrontal cortex, and cerebellum volumes reduction and correlation with core symptoms help in assessment of the pathophysiology of schizophrenia.

*Key Words:* *Volumetric – MRI – Schizophrenia.*

## Introduction

**SCHIZOPHRENIA** is a severe and disabling psychiatric illness, characterized by a heterogeneous course often with clinical deterioration and poor outcome. The disease affects around 0.3-0.7% of people at some point in their life or 24 million people worldwide [1]. Schizophrenia causes approximately 1% of worldwide disability adjusted life years [2].

Schizophrenia is often defined in terms of negative and positive symptoms. Negative symptoms are lack of normal emotional responses or other thought actions. Positive symptoms include disordered thoughts and speech, delusions and hallucinations. They usually include dampened emotion and affect, scarcity of speech (alogia), reduced motivation or ability to experience pleasure (anhedonia), lack of wish to form relationships (asociality), and absence of motivation (avolition) [2].

Volumetric MRI studies of cerebellum and vermis in schizophrenic patients showed greater volume of vermis volume than control group, which reveal significant correlation with positive symptoms severity, thought disorder and verbal logical memory impairment. Also results revealed more cerebellar hemispheric volume asymmetry in schizophrenic patients [3].

Hippocampal volume reduction have been reported in patients with schizophrenia by Several magnetic resonance imaging studies [4].

During cognitive activation, three patterns of abnormal cerebral blood flow have been demonstrated in recent functional imaging studies. First, decreased blood flow in the dorsolateral prefrontal cortex was found in schizophrenia patients with impairment of working memory functions. Second, dysfunction of prefrontal-thalamic-cerebellar circuitry was detected in cognitive dysmetria. Third, increased blood flow in limbic, medial temporal lobe and subcortical structures was detected in auditory hallucinations and psychotic symptoms [5].

---

*Correspondence to:* Dr. Rasha El-Shafey,
E-Mail: drrashaelshafey@yahoo.co.uk

The aim of the study is to find correlation between volumes of Prefrontal Cortex (PFC), Hippocampus, (HC) and Cerebellum (CRM) and core symptoms of schizophrenia (positive, negative and cognitive).

## Patients and Methods

The study included twenty age matched healthy control group and thirty patients with schizophrenia were referred to Radiodiagnosis Department during the period from January 2014 to February 2015.

Approval of Research Ethics Committee (REC) and informed written consent were obtained from all participants either from the patient or the legal sponsor in the study. All patients related informations were kept confidential.

The patients of schizophrenia were diagnosed according to the revised fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) [6].

*Inclusion criteria:*

- Age: 25-40 years old.

- Duration of schizophrenia illness: Less than 24 months.

*Exclusion criteria:*

- Other co-morbid DSM-IV disorder.

- First degree relatives with a diagnosis of mood disorder.

- Neurological disorders including dementia or any current medical illness particularly those with possible impact on the brain volume or mental functions.

Patient and/or his legal sponsor will keep the right to withdraw at any step of the research. The patients in the research will be continuously observed all the time of the research.

*A- Clinical evaluation:*

* General physical examination to rule out the exclusion criteria mentioned.

* Clinical psychiatric evaluation using structured interview designed for the study and adapted from Clinical Assessment of Symptom and History (CASH) [7].

*B- Psychometric procedures:*

*The following scales were administered:*

- Positive and Negative Syndrome Scales (PANSS) [8].

- Folstein mini mental state examination.

- Wechsler Memory Scale (WMS) [9].

- Trail Making test [10].

*C- Volumetric MRI brain study:*

*Image acquisition and postprocessing:*

The images were acquired using a 1.5-T MRI scanner (GE Medical Systems, Milwaukee) with NV array haed and neck coil (16 channel). Sedation was needed for 10 uncooperative patients.

A three-dimensional T 1 spoiled gradient sequence was used for volumetric study.

The following parameters were used for the SPGR images: Repetition Time (TR)=24msec, echo time (TE)=3msec, nutation angle=45º, repetition=1, acquisition matrix=256 X 256 X 124, field of view=24cm, voxel dimensions= 0.9365 X 0.9365 X 3mm).

Fast fluid-attenuated inversion recovery [TE/TR/NEX] 142/8000/1; inversion time, 2100ms) and diffusion weighted images [TE/TR/NEX] 93/10,000/1 with diffusion sensitivities of b=1000 $s/mm^2$ and b=0s/mm$^2$) were obtained to clarify exclusion criteria.

*Volumetric analysis:*

Volumetric analysis was done using 3D Slicer software ver. 4.2.2-1 developed by Harvard University and approved for medical research (http:// www.slicer.org/). Which is a multiplatform, free open source software package for visualization and medical image computing.

The targeted areas were segmented in a semi-automatic way by tracing their outlines manually, and the software was preset not to exceed the outlines of the region of interest by assigning the MR numbers of the targeted areas. A quantification process was run after each brain slice containing the nuclei or regions of interest was segmented, as well as a 3-D graphical model of it. The data was validated by reviewing with SPL-PNL Brain Atlas (developed by Talos et al. 2008) [11]. The advantage of semiautomatic methods was to provide accurate approach for grey matter segmentation because they combine the automatic techniques with a previous operator information of the location of grey matter, shape and anatomical boundaries.

Measurement of the hippocampal volume ROI analysis: It starts beneath the amygdala and end posteriorly where the crura of the fornices diverge from the lateral ventricles. The hippocampus

composed of the hippocampus proper, the dentate gyrus, and the subicular complex [12,13].

### Dorso-Lateral Prefrontal Cortex (DLPFC) ROI:

The approved anatomical landmarks for areas 46 and 9 (plus transitional areas 46-45, 46-10, 9-45, and 9-8), area 46 located in the middle frontal gyrus, area 9 is consistently located in the superior frontal gyrus. Tracing start on the slice anteriorly located to the most anterior one where corpus callosum could be seen. Tracing was done from posterior to anterior and traced where the superior and middle frontal gyrus could be noted anteriorly [11].

### Cerebellum ROI:

The cerebellar hemispheres were splitted in the sagittal plane between the medial vermis. Axial and coronal planes were used also for best adjustment. Separation from the brain stem was achieved by cutting the cerebellar peduncles at their entrance into the cerebellum [14].

### Statistical analysis:

The mean and standard deviation by SPSS V. 16. Analysis of variance [ANOVA] tests. Determination of the significance between two groups was done by Tukey's test: According to the SPSS windows computer program. Quantitative comparison between different times in the same group was done by ANOVA test. $p$-value <0.05 was considered significant.

## Results

Correlation of the regional brain volume with psychopathology and cognition in 20 schizophrenic patient controlled with age:

A- *Positive and negative symptoms scale:* Statistically significant negative correlation between positive and negative symptoms and (hippocampus, cerebellum and the prefrontal cortex volumes). While no significant correlation between general symptoms and any of the studied volumes, (Table 1).

B- While correlation between Wechsler Memory Scale (WMS) and the studied volumes revealed statistically significant positive correlation between auditory memory (immediate and delayed) and (left prefrontal cortex and vermis), with statistically significant positive correlation between immediate visual memory and the left prefrontal cortex volume and statistically significant positive correlation between delayed visual memory and right prefrontal cortex. Statistically significant negative correlation between delayed visual memory and (hippocampus

(right and left) & left cerebellum) (Table 2), Figs. (1,2).

Evidence of decrease the volume of the cerebellum, drosolateral prefrontal cotex and hyppocampus volumes as compared with the control group Fig. (2).

*NB:* The represented images does not include all images of each part measured.

C- Statistically significant positive correlation between minimintal state test results and both right and left prefrontal cortex volume as well as the vermis volume Fig. (3).

Table (1): Correlation between positive and negative symptoms and (hippocampus, cerebellum and the prefrontal cortex volumes).

| PANSS | Perfrontal cortex | | Hippocampus | | Cerebellum | | Vermis |
|---|---|---|---|---|---|---|---|
| | Left | Right | Left | Right | Left | Right | |
| *Positive:* | | | | | | | |
| r | –0.323 | –0.453 | –0.595 | –0.595 | –0.220 | 0.123 | 0.595 |
| p | 0.178 | 0.051 | 0.007 | 0.007 | 0.365 | 0.616 | 0.007 |
| *Negative:* | | | | | | | |
| r | 0.216 | 0.101 | –0.050 | –0.050 | –0.048 | –0.825 | –0.769 |
| p | 0.374 | 0.681 | 0.839 | 0.839 | 0.844 | 0.001 | 0.001 |
| *General:* | | | | | | | |
| r | 0.066 | –0.406 | –0.352 | –0.352 | 0.389 | –0.115 | 0.276 |
| p | 0.789 | 0.085 | 0.139 | 0.139 | 0.100 | 0.640 | 0.253 |

Table (2): Correlation between Wechsler Memory Scale (WMS) and the studied volumes.

| | Perfrontal cortex | | Hippocampus | | Cerebellum | | Vermis |
|---|---|---|---|---|---|---|---|
| | Left | Right | Left | Right | Left | Right | |
| *Auditory immediate:* | | | | | | | |
| r | 0.585 | 0.157 | 0.010 | 0.010 | –0.179 | 0.136 | 0.645 |
| p | 0.009 | 0.521 | 0.966 | 0.966 | 0.463 | 0.580 | 0.003 |
| *Auditory delayed:* | | | | | | | |
| r | 0.525 | 0.108 | –0.069 | –0.069 | –0.337 | 0.185 | 0.781 |
| p | 0.021 | 0.659 | 0.779 | 0.779 | 0.159 | 0.448 | 0.001 |
| *Visual immediate:* | | | | | | | |
| r | 0.551 | –0.095 | –0.367 | –0.367 | –0.118 | –0.396 | 0.385 |
| p | 0.014 | 0.700 | 0.122 | 0.122 | 0.629 | 0.093 | 0.103 |
| *Visual delayed:* | | | | | | | |
| r | 0.275 | 0.523 | –0.651 | –0.651 | –0.551 | –0.249 | 0.333 |
| p | 0.255 | 0.022 | 0.003 | 0.003 | 0.014 | 0.304 | 0.164 |
| *Working memory:* | | | | | | | |
| r | 0.348 | 0.052 | –0.272 | –0.272 | 0.267 | 0.212 | 0.650 |
| p | 0.144 | 0.832 | 0.260 | 0.260 | 0.268 | 0.383 | 0.003 |
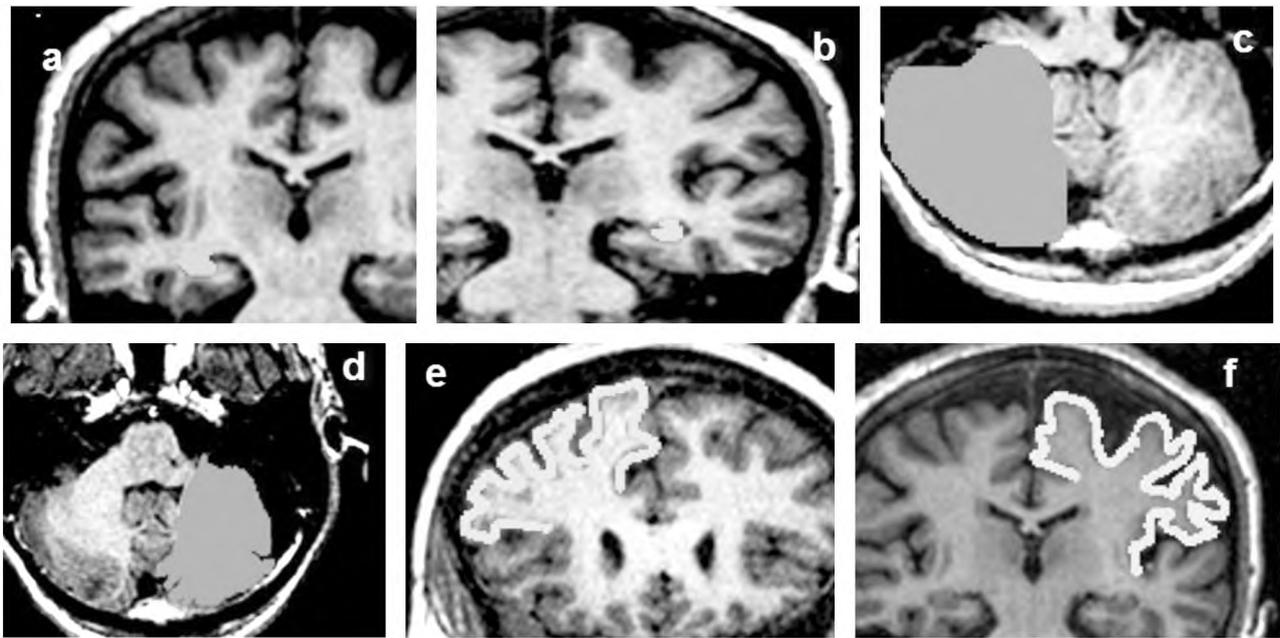
Fig. (1): Control case, (A,B) Right and left Hippocampus, (C,D) Right and left cerebellum, (E,F) Right and left DLFPC.



(A)

(B)

(C)

(D)

(E)

(F)
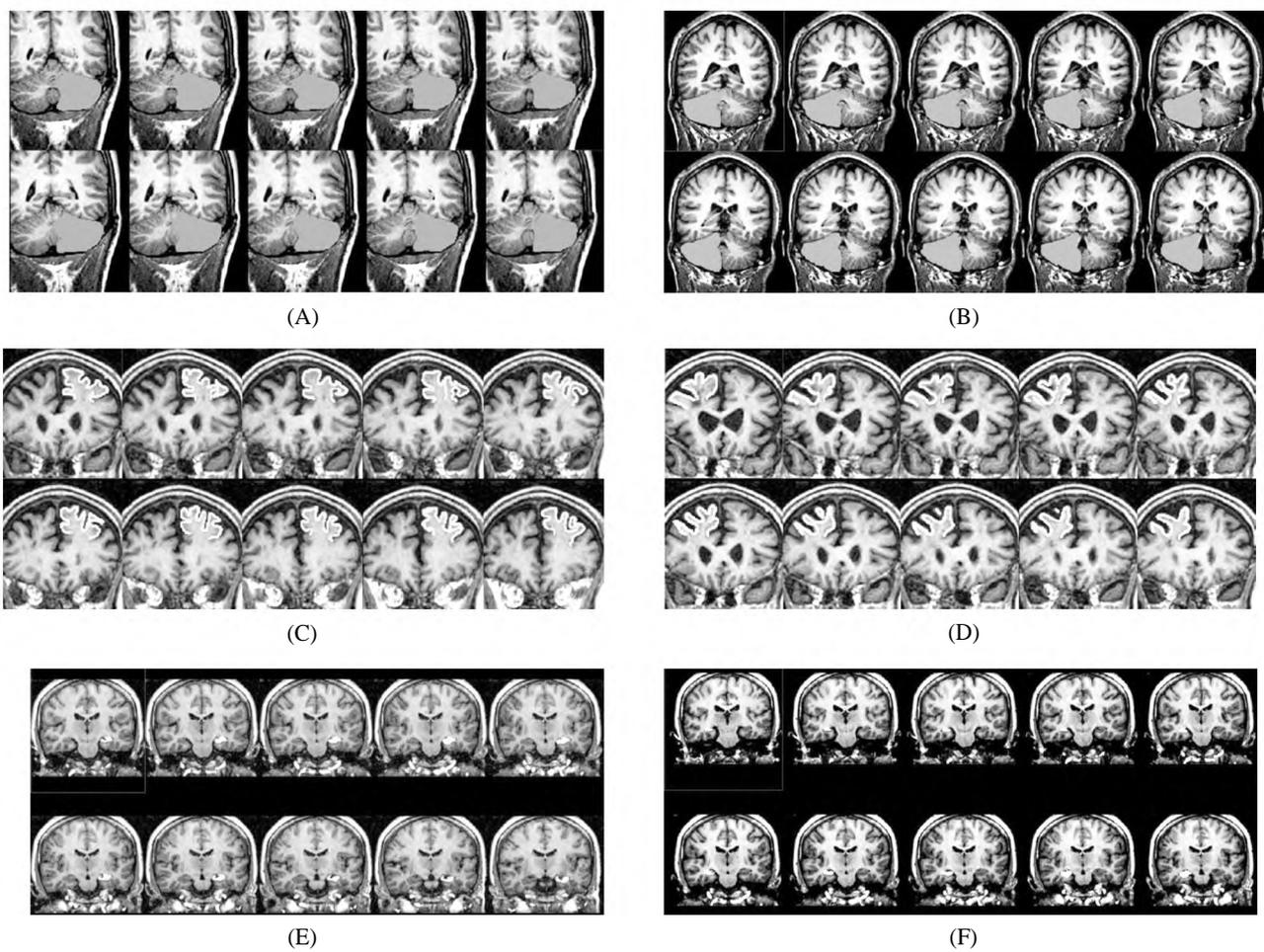
Fig. (2): MRI volumetric measurement of male patient, 30 years old, known to be schizophrenic since 1.5 year, (A,B) Left and right cerebellum, (C,D) Left and right dorsolateral prefrontal cortex (E,F) Left and right Hippocampus.
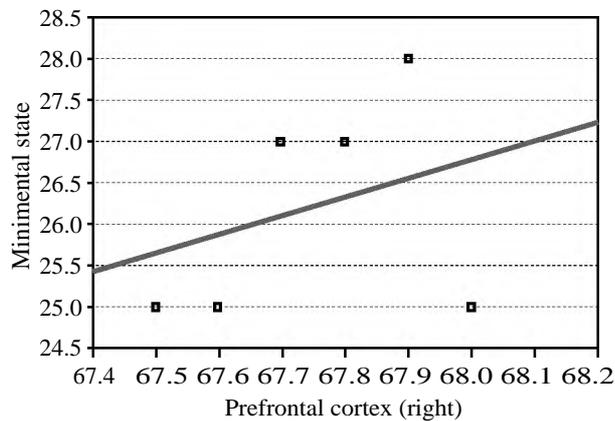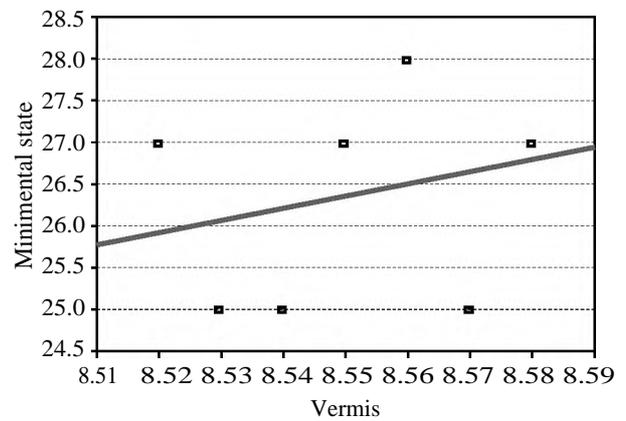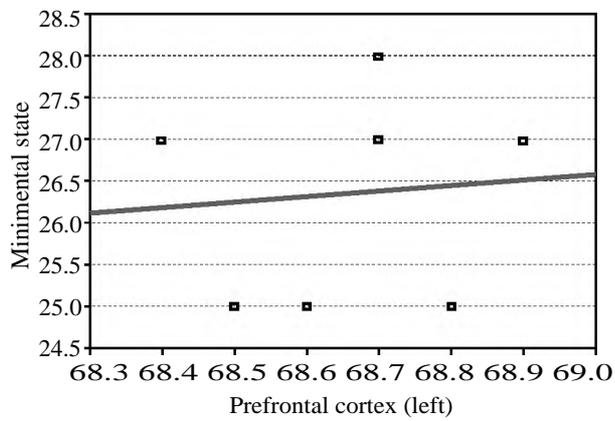
Fig. (3): Correlation between minimintal state test results and both right and left prefrontal cortex volume as well as the vermis volume.

## Discussion

Schizophrenia, with an early age of onset, is a chronic psychiatric debilitating disorder, affects an approximated 1 % of the community. it is serious to establish radiologic markers to diagnose it and advance our knowledge of its biology [15,16].

Several magnetic resonance imaging studies have reported brain volume changes in patients with schizophrenia [17]. Our study results reveal a significant reduction in right hippocampus volume in schizophrenic patients with a $p$-value of 0.042, also our results report reduction in left hippocampus volume although it does not reach statistical significance. These results partially agree with Adriano and colleges who found that there was significant difference in both right and left hippocampus volumes with a $p$-value of <0.0001. This partial difference between our study and Adriano and colleges' study may be due to smaller number of patients in our study [18].

Also there is reduction in both right and left cerebellar volumes with a $p$-value of 0.025 and 0.041 respectively. Our results agree with Christina Bottmer and colleges that proved that there is significant reduction in cerebellar volume among schizophrenics with a $p$-value of <0.0001 [19].

On studying the vermis volume there is significant reduction in its volume in schizophrenic patients with a $p$-value of 0.02. Our study agree with Tetsuya Ichimiya and colleges in the point that the volume of the vermis was significantly reduced in the schizophrenic group relative to the control group but we don't agree with them that there is no significant differences were found in the volumes of other cerebellar structures [20].

On comparing the right and left prefrontal cortex size in patients and controls we found that there is a significant reduction in their size in schizophrenic patients with a p value of 0.006 and 0.009 respectively. Our results don't agree with Cynthia G. and colleges results who showed no significant differences were found between schizophrenic and control subjects in mean values for prefrontal white or gray matter on either the right or the left side [21]. This may be due to application of their study to few number [14] and to males only. Our results are in accordance to Raquel E. Gur and colleges who found that Reduced prefrontal gray matter volume was observed in patients. The

reduction was evident for the dorsolateral area in men (9%) and women (11%), for the dorsomedial area only in men (9%) [22].

*In Conclusion:*

Shizophrenic patients has cognitive impairment as regard to excutive function and working memory, as regard immediate and delayed both auditory and visual memory. This study indicates that the volume of the Hippocampus, cerebellum and prefrontal cortex volumes (compared to healthy control group) are reduced in patients with schizophrenia, and is suggested to be related to the pathophysiology of the disease.

Limitation of this study is prolonged time of the MR volumetric protocol, also the statistical analysis power is decreased by rather little cases number decrease.

A strength of our study is that we focused on the age between 20-40 years old with duration of illness not more than 24 months.

## References

1- SMITH T., WESTON C. and LIEBERMAN J.: Schizophrenia (maintenance treatment). Am. Fam. Physician, 82 (4): 338-9. PMID 20704164, 2010.

2- KNEISL C. and TRIGOBOFF E.: Contemporary Psychiatric-Mental Health Nursing. 2 nd edition. London: Pearson Prentice Ltd. P. 371: 244-50, 2009.

3- SZENDI I., SZABÓ N., DOMJÁN N., et al.: A New Division of Schizophrenia Revealed Expanded Bilateral Brain Structural Abnormalities of the Association Cortices. Frontiers in Psychiatry, 8, 127. http://doi.org/10.3389/fpsyt.2017.00127, 2017.

4- ARDEKANI B.A., BAPPAL A., D'ANGELO D., et al.: Brain morphometry using diffusion-weighted magnetic resonance imaging: Application to schizophrenia. Neuroreport, 16 (13): 1455-9, 2005.

5- FUJIKI R., MORITA M. and UCHIMURA N.: Reduced prefrontal cortex activation using the Trail Making Test. Neuropsychiatric Dis. Treat., 9: 875-85, 2013.

6- WASHINGTON D.C.: American Psychiatric Association. Diagnostic and statistical manual of mental disorders (4thed., text rev.) 2000.

7- ANDREASEN N.C., ENDICOTT J., SPITZER R.L., et al.: The family history method using diagnostic criteria:Reliability and validity. Archives of General Psychiatry, 34: 1229-35, 1977.

8- KAY S.R., FISZBEIN A. and OPLER L.A.: The Positive and Negative Syndrome Scale (PANSS) for schizophrenia. Schizophr Bull, 13 (2): 261-76, 1987.

9- WECHSLER D.: Wechsler Memory Scale-Revised. Psychological Corporation, New York, 1987.

10- REITAN R.M.: Validity of the Trail Making test as an indicator of organic brain damage. Percept. Mot. Skills, 8: 271-6, 1958.

11- TALOS I.F., JAKAB M., KIKINIS R., et al.: SPL-PNL Brain Atlas. SPL-PNL March, 641-2, 2008.

12- JACK Jr. C.R., THEODORE W.H., COOK M., et al.: MRI-based hippocampal volumetrics: Data acquisition, normal ranges, and optimal protocol. Magnetic Resonance Imaging, 13: 1057, 1995.

13- DUVERNOY H.M.: "Introduction" [93]. The Human Hippocampus, Functional Anatomy, Vascularization and Serial Sections with MRI. (3 rd ed.) Berlin Heidelberg: Springer Verlag, 2005.

14- SANDOK E.K., O'BRIEN T.J., JACK C.R., et al.: Significance of cerebellar atrophy in intractable temporal lobe epilepsy: A quantitative MRI study. Epilepsia, 41: 1315-20, 2000.

15- ALNAES D., TOBIAS M., DENNIS V., et al.: The dark side of the mean: Brain structural heterogeneity in schizophrenia and its polygenic risk, 10.1101/407890, 2008.

16- HUHTANISKA S., JÄÄSKELÄINEN E., HIRVONEN N., et al.: Long-term antipsychotic use and brain changes in schizophrenia-a systematic review and meta-analysis. Hum Psychopharmacol Clin. Exp., 32: e2574. https:// doi.org/10.1002/hup.2574, 2017.

17- ARDEKANI B.A., BAPPAL A., D'ANGELO D., et al.: Brain morphometry usin diffusion-weighted magnetic resonance imaging: Application to schizophrenia. Neuroreport, 16 (13): 1455-9, 2005.

18- ADRIANO F., CALTAGIRONE C. and SPALLETTA G.: Hippocampal Volume Reduction in First-Episode and Chronic Schizophrenia: A Review and Meta-Analysis The Neuroscientist, Apr., 18 (2): 180-200, 2012.

19- BOTTMER C., BACHMANN S., PANTEL J., et al.: Reduced cerebellar volume and neurological soft signs in first-episode schizophrenia. Psychiatry Res. Dec., 30, 140 (3): 239-50, 2005.

20- ICHIMIYA T., OKUBO Y., SUHARA T., et al.: Reduced volume of the cerebellar vermis. Neuroleptic-naive schizophrenia Volume 49, Issue 1, 1 Pages 20-27, 2001.

21- CYNTHIA G., MARTHA E., HIROTO H., et al.: Prefrontal Cortex and Schizophrenia: A Quantitative Magnetic Resonance Imaging Study Arch. Gen. Psychiatry, 52 (4): 279-88, 1995.

22- GUR R.C., ALSOP D., GLAHN D., et al.: An fMRI study of sex differences in regional activation to a verbal and a spatial task. Brain Lang, 74: 157-70, 2000.

# التغيرات الحجمية بالرنين المغناطيسى على المخ فى مرضى الفصام

────

الفصام العقلى يعد من آشد الإضطرابات النفسية وآوسعها إنتشارا. حيث يصيب نحو ٢٤ مليون شخص فى كل آنحاء العالم. وغالبا ما يبدأ المرض فى سن الشباب (بين العشرين والثلاثين من العمر) مما يجعله سببا رئيسيا من آسباب العجز. ويوصف الفصام غالبا فى شكلين رئيسيين: آحدهما هو الأعراض الجانبية، مثل الضلالات والهلاوس وإضطراب التفكير والكلام، والآخر هو الأعراض السلبية، وتعنى الخلل فى الإستجابة العاطفية والإجتماعية وعدم إحساس بالمتعة وإنخفاض الدافعية. على الرغم من وجود عوامل جينية وبيئية مشاركة فى التسبب بالمرض، فإن السبب الحقيقى لمرض الفصام لا يزال مجهولا. وقد إفترض العلماء منذ القدم وجود خلل دماغى، خاصة فى الفصين اجبهى والصدغى من المخ، مرتبط بالمرض.

الهدف من البحث: هو إستكشاف التغيرات الحجمية فى المخ لكل من قشرة الحصين، المخيخ والفص الجبهى بين مرضى الفصام. دراستنا سوف تستكشف آيضا إذا كانت ترتبط من آى الأعراض السلبية آو الإيجابية لمرض الفصام مع آى من التغيرات الممكنه.

هذه الدراسة تشتمل على ثلاثين ممن يعانون من مرض الفصام العقلى على آن تتراوح آعمار المرضى ما بين عشرين إلى آربعين سنة وآن لا تزيد فترة المريض عن آربعة وعشرين شهرا مع وجود مجموعة ضابطة سليمة مكونة من عشرين فرد.

وخضعت جميع الحالات التى تمت دراستها إلى:

• تاريخ طبى تفصيلى.

• فحص إكلينيكى وعصبى شامل مع الإختبارات المعملية الروتينية لتحقيق معايير الإستبعاد المذكورة سابقا.

• تقييم الأعراض الإيجابية والأعراض السلبية لمرض الفصام العقلى.

• تقييم الوظائف التنفيذية المعرفية وغيرها.

• التصوير بالرنين المغناطيسى للمخ لكل من الحصين، والمخيخ، وقشرة الفص الجبهى.

المستخلص من البحث: هناك علاقة ذات مدلول إحصائى بين الإختبارات التى تم إجراؤها وحجم قشرة المخيخ وقشرة الفص الجبهى وحجم الحصين وظهر ذلك من خلال التحليل الإحصائى للنتائج.