Volumetric Brain MRI Changes in Schizophrenic Patients

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Aims and objectives

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 described in terms of positive and negative (or deficit) symptoms. Positive symptoms include delusions, disordered thoughts and speech; tactile, auditory, visual, olfactory or gustatory hallucinations. Negative symptoms are deficits of normal emotional responses or other thought processes. They commonly include flat or blunted affect and emotion, poverty of speech (alogia), inability to experience pleasure (anhedonia), lack of desire to form relationships (asociality), and lack of motivation (avolition)(2).

Volumetric MRI studies of cerebellum and vermis in schizophrenic patients show that 1) vermis volume was greater in patients with schizophrenia than in normal subjects, 2) greater vermis white matter volume in the patients with schizophrenia significantly correlated with severity of positive symptoms and thought disorder and with impairment in verbal logical memory, and 3) patients with schizophrenia showed a trend for more cerebellar hemispheric volume asymmetry(3).

Several magnetic resonance imaging studies have reported hippocampal volume reduction in patients with schizophrenia(4).

More recent functional imaging studies have demonstrated three patterns of abnormal cerebral blood flow during cognitive activation. First, impairment of working memory functions in schizophrenia has been associated with decreased blood flow in the dorsolateral prefrontal cortex. Second, cognitive dysmetria, the inability to receive and process information rapidly, has been associated with a dysfunction of prefrontal-thalamic-cerebellar circuitry. Third, auditory hallucinations and the experience of psychotic symptoms have been associated with increased blood flow in medial temporal lobe, limbic and subcortical structures. Recent studies have mapped the neuroanatomy of memory to a network of cortical and subcortical structures in the human brain(5).

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).
Methods and materials

The study include twenty age matched healthy control group and thirty patients with schizophrenia were referred to radiodiagnosis department from Neuropsychiatry departments, Tanta University.

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: 1-Age: 25-40 years old
2-Duration of illness:less than 24 months

EXCLUSION CRITERIA:
1- Other co-morbid DSM-IV disorder
2- First degree relatives with a diagnosis of mood disorder
3- 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:
1. Positive and Negative Syndrome Scales (PANSS)(8)
2. Folstein Mini Mental State Examination(9)
3. Wechsler Memory Scale (WMS)(10)

4. Trail Making test(11)

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 head and neck coil (8 channel). Sedation was needed for 10 uncooperative patients.

A three-dimensional T1 spoiled gradient sequence was used.

The following parameters were used for the SPGR images: echo time (TE) =3 msec, repetition time (TR) =24 msec, repetition=1, nutation angle=45°, field of view=24 cm, acquisition matrix=256×256×124, voxel dimensions= 0.9365×0.9365×3 mm, resolution 1mm×1mm ×1 mm). This protocol resulted in high spatial-resolution images with extremely good gray-white matter contrast. Fast fluid-attenuated inversion recovery [TR/TE/NEX] 8000/142/1; inversion time, 2200 ms) and diffusion weighted images (Diffusion-weighted imaging was done using single-shot spin-echo echo-planar sequence ([TR/TE/NEX] 10,000/93/1 with diffusion sensitivities of b = 0 s/mm2 and b = 1000 s/mm2) were obtained to exclude cerebrovascular disease and other causes of exclusion criteria.

Volumetric analysis:

Volumetric analysis of the dorsolateral prefrontal cortex, cerebellum and hippocampus was performed using 3D Slicer software ver. 4.2.2-1 which is a multiplatform, free open source software package for visualization and medical image computing developed by Harvard University and approved for medical research (http://www.slicer.org/) (fig. 1). And also on workstation with software (Functool, GE Healthcare, Milwaukee, WI, USA).

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. After each brain slice containing the nuclei or regions of interest was segmented, a quantification process was run which rendered the volume of the structure in focus as well as a 3-D graphical model of it. The data is validated by comparison with SPL-PNL Brain Atlas (developed by Talos et al.2008)(12) semiautomatic methods. They provide a more realistic approach for grey matter segmentation because they combine the automatic techniques with a prior operator knowledge of the grey matter location, anatomical boundaries, and shape.

Measurement of the hippocampal volume ROI analysis: Tracing of the hippocampus started rostrally where the hippocampus first appears below the amygdala and ended posteriorly in the section where the crura of the fornices depart from the lateral wall of the lateral ventricles. The hippocampus included the dentate gyrus, the hippocampus proper
and the subicular complex. Each hippocampus was traced independently with reference to previous hippocampal MR volumetric studies and the hippocampal atlas (13, 14).

Dorso-lateral prefrontal cortex (DLPFC) ROI: The adopted anatomical landmarks for areas 9 and 46 (plus transitional areas 9-8, 9-45, 46-10, and 46-45), area 9 is consistently located in the superior frontal gyrus, whereas area 46 can be found in the middle frontal gyrus. Tracing start on the slice located immediately anterior to the most rostral one where corpus callosum could be seen. Tracing was performed from posterior to anterior and continued until the most anterior slice where the superior and middle frontal gyrus could be distinguished (12).

cerebellum ROI:

The cerebellar hemispheres were bisected between the two smallest sections through the medial vermis in the sagittal plane. When this boundary was distorted or curved, adjustments were made by using simultaneous visualization in the axial and coronal planes. Disarticulation from the brain stem was performed by transecting the cerebellar peduncles along the plane of their entrance into the cerebellum. Using this technique, the deep cerebellar nuclei were retained in the measured volumes whereas the peduncles were largely excluded (15).

Statistical analysis

Statistical presentation and analysis of the present study were conducted, using the mean and standard deviation by SPSS V.16. Analysis of variance [ANOVA] tests and Tukey's test was used to determine the significance between two groups: according to the computer program SPSS for Windows. ANOVA test was used for comparison among different times in the same group in quantitative data. p Value < 0.05 was considered significant.
Fig. 1: 3D Slicer version 4.2.2-1 software

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Results

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

A. Positive and negative symptoms scale:

There were statistically significant negative correlations between positive and negative symptoms and (cerebellum and the prefrontal cortex volume). There was 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 correlations 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).

C: There was a statistically significant positive correlation between Minimintal state test results and both right and left prefrontal cortex volume and also the vermis volume (table 3).

Case 1: MRI Volumetric measurement in one of the control group: figure 2 (a, b) right & left Hippocampus, (c, d) right and left cerebellum, (e, f) right and left DLFPC.

Case 2: male patient, 30 years old, known to be schizophrenic since 1.5 years.

MRI Volumetric measurement of left and right cerebellum {fig. (3), (4)}, left and right dorsolateral prefrontal cortex {fig. (5), (6)}, left and right Hippocampus {fig. (7), (8)}.

Evidence of a decrease in the volume of the cerebellum, dorsolateral prefrontal cortex, and hippocampus in comparison with the control group. (figure 2)

NB: the represented images does not include all images of each part measured.
<table>
<thead>
<tr>
<th>PANSS</th>
<th>Prefrontal cortex</th>
<th>Hippocampus</th>
<th>Cerebellum</th>
<th>Vermis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Left</td>
<td>Right</td>
<td>Left</td>
<td>Right</td>
</tr>
<tr>
<td>Positive</td>
<td>0.789</td>
<td>0.085</td>
<td>0.139</td>
<td>0.139</td>
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<tr>
<td></td>
<td>0.051</td>
<td>0.681</td>
<td>0.839</td>
<td>0.839</td>
</tr>
<tr>
<td>Negative</td>
<td>0.216</td>
<td>0.101</td>
<td>-0.050</td>
<td>-0.050</td>
</tr>
<tr>
<td></td>
<td>0.374</td>
<td>0.681</td>
<td>0.839</td>
<td>0.839</td>
</tr>
<tr>
<td>General</td>
<td>0.066</td>
<td>-0.406</td>
<td>-0.352</td>
<td>-0.352</td>
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<tr>
<td></td>
<td>0.789</td>
<td>0.085</td>
<td>0.139</td>
<td>0.139</td>
</tr>
</tbody>
</table>

Table 1: Correlation between Positive and negative symptoms scale (PANSS) and the studied volumes:

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<table>
<thead>
<tr>
<th>WMS</th>
<th>Prefrontal cortex</th>
<th>Hippocampus</th>
<th>Cerebellum</th>
<th>Vermis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Left</td>
<td>Right</td>
<td>Left</td>
<td>Right</td>
</tr>
<tr>
<td>Auditory immediate</td>
<td>0.585</td>
<td>0.157</td>
<td>0.010</td>
<td>0.010</td>
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<tr>
<td></td>
<td>0.009</td>
<td>0.521</td>
<td>0.966</td>
<td>0.966</td>
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<tr>
<td>Auditory delayed</td>
<td>0.525</td>
<td>0.108</td>
<td>-0.069</td>
<td>-0.069</td>
</tr>
<tr>
<td></td>
<td>0.021</td>
<td>0.659</td>
<td>0.779</td>
<td>0.779</td>
</tr>
<tr>
<td>Visual immediate</td>
<td>0.551</td>
<td>-0.095</td>
<td>-0.367</td>
<td>-0.367</td>
</tr>
<tr>
<td></td>
<td>0.014</td>
<td>0.700</td>
<td>0.122</td>
<td>0.122</td>
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<tr>
<td>Visual delayed</td>
<td>0.275</td>
<td>0.523</td>
<td>-0.651</td>
<td>-0.651</td>
</tr>
<tr>
<td></td>
<td>0.255</td>
<td>0.022</td>
<td>0.003</td>
<td>0.003</td>
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<tr>
<td>Working memory</td>
<td>0.348</td>
<td>0.052</td>
<td>-0.272</td>
<td>-0.272</td>
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<tr>
<td></td>
<td>0.144</td>
<td>0.832</td>
<td>0.260</td>
<td>0.260</td>
</tr>
</tbody>
</table>

Table 2: Correlation between Wechsler memory scale (WMS) and the studied volumes

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**Fig. 1:** 3D Slicer version 4.2.2-1 software

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Fig. 3: MRI Volumetric measurement of left cerebellum

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Fig. 4: MRI Volumetric measurement of right cerebellum

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Fig. 5: MRI Volumetric measurement of left dorsolateral prefrontal cortex

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Fig. 6: MRI volumetric measurement of right dorsolateral prefrontal cortex

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Fig. 7: MRI Volumetric measurement of left hippocampus

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Fig. 8: MRI Volumetric measurement of right hippocampus

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Table 3: correlation between minimental state and left, right prefrontal cortex and vermis

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**Fig. 2:** MRI Volumetric measurements in one of control group

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Conclusion

Schizophrenia, which is a chronic debilitating psychiatric disorder with an early age of onset, affects an estimated 1% of the population\(^{16}\).

Its direct treatment-related costs and indirect, mostly unemployment-related costs are estimated at $23 billion and $32 billion, respectively, in the United States alone\(^{2}\). To facilitate new treatments for schizophrenia, it is imperative to advance our understanding of its biology and develop radiologic markers with which to monitor it\(^{17}\).

Several magnetic resonance imaging studies have reported brain volume changes in patients with schizophrenia\(^{4}\).

There was a significant reduction in right hippocampus volume in schizophrenic patients with a p value of 0.042 also there was reduction in left hippocampus volume although it didn't reach statistical significance. These results partially agree with Adriano and colleges who found that there is 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 cases 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. Wible 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 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%)\(^{22}\).

so in conclusion
1- Schizophrenic patients have cognitive impairment as regards to

# Executive function

# Working memory, immediate and delayed both auditory and visual memory

2- 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 and expression of early neurodevelopmental compromise, reflecting the degree of genetic liability to schizophrenia.

**Limitation of this study** is time consuming protocol of MR volumetry, also relatively low number of cases decrease the power of statistical analysis. Larger sample size and longitudinal study are needed to confirm our findings.

**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.

Furthermore, most of the participants were not resistant to treatment and had relatively limited exposure to psychotropic drugs.
Personal information

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References


