Hippocampal volume in chronic schizophrenia and first episode drug-naïve psychotic patients

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Abstract:

Reduced hippocampal volume is a structural abnormality frequently found in Schizophrenia. The reduction may be a consequence of neurodevelopment events preceding the illness and/or a result of the disease process itself. Our aim is to examine whether hippocampal volume reduction is present early in the disease or it is the effect of chronicity. Magnetic resonance imaging brain scans of patients in their first episode psychosis were compared with those of chronically ill schizophrenic patients. Scans for controls matched to both patient groups were also performed. Symptoms severity was also assessed. We found that both groups of patients had smaller hippocampal volumes compared to controls. The reduction in volume was greater in chronic than in acute young patients. The findings support both hypotheses of developmental and progressive hippocampal reduction in schizophrenia.

Introduction:

Schizophrenia is a disabling illness, but its etiology remains poorly understood ***(Silver and Davis, 2004).*** It remains to be determined whether schizophrenia is neurodegenerative process that beings at about the time of symptom onset and manifests as progressive volumetric loss, or whether it is better characterized as neurodevelopmental process that results in abnormal brain volume beginning at an early age ***(Maynard et al, 2001).***

Neurodevelopmental models postulated an important role for aberrant hippocampal morphology in the patho-physiology of schizophrenia. There is considerable evidence from postmortem (***Arnold et al 1995***; ***Benes et al, 1991; Jeste & Lohr, 1989 Kovelman et al, 1984***) and magnetic resonance imaging (MRI) studies ***(Bogerts et al, 1993; Shenton et al, 1992; Bogerts et al, 1990)*** that patients with schizophrenia have hippocampal structural abnormalities. About 4% reduction in bilateral hippocampal volumes had been identified in patients with schizophrenia relative to controls ***(Nelson et al, 1998).***

In recent years with the advent of brain imaging methods such as MRI, it has become possible to study patients during their first episode of psychosis, before disease effects are obscured by the confounding influences typical of cases of chronic schizophrenia ***(Shenton et al, 2001).*** Studies in first episode psychosis have inconsistently reported brain volume changes in that group of patients, relative to control. While some studies reported smaller hippocampi ***(Gur et al, 2000a)***, others reported no difference in hippocampal volume in first episode patients relative to control (***Chan et al, 2002).***

Hippocampal volume reduction has been reported in unaffected first degree relatives of schizophrenic patients ***(Seidman et al, 2002).*** However, this finding is also inconsistent. More recent studies ***(Velakoulis et al, 2006; McDonald et al, 2006; Schulze et al, 2003)*** revealed no

volume reduction within the ultra high risk group.

The developmental versus neurotoxic hypotheses for schizophrenia were discussed by ***Cotter and Pariante 2002*** who concluded that brain changes founded at psychosis onset or possibly after are not purely developmental and not specific for schizophrenia.

Velakoulis, et al 1999 identified smaller hippocampal volumes bilaterally with chronic schizophrenia and with first-episode patients than control, but also noted its non specificity where it is present within schizophrenic and non schizophrenic affective groups. On the other hand, ***McDonald and colleges 2006,*** reported hippocampal volume reduction only in schizophrenic patients, but not in bipolar disorder patients or in their unaffected relatives.

In contrast, ***Delisi et al 1991*** found no differences in brain volume at illness onset and this occurred with reduction of whole brain volume after 4 years. These reports as well as results of right hippocampal volume reduction association with illness duration may raise neurotoxic hypothesis of schizophrenia ***(Volkoulis, et al 1999).***

This inconsistency in results could be explained by many factors such as technical variability, small sample size, and/or failure to match for age, gender or handedness.

Objectives:

Although many quantitative magnetic resonance imaging studies have found volume reduction in the hippocampi of patients with schizophrenia compared with those of normal control subjects, others have not. Therefore, it remains questionable.

Aim of the Study:

Our aim is to study hippocampal volume in both chronic schizophrenia and first episode drug-naïve psychotic patients. Then, test the illness duration, severity and drug treatment on the brain structural findings.

Methods:

The study had been conducted at the Psychological Medicine Hospital, Kuwait, over 6 month period from the 1st of August 2005 to 31st of January 2006. Written informed consent was a prerequisite for participation. Patients recruited had been divided into two main groups:

- ***Group I (Drug – naïve patients with first episode psychosis):***

A total of 32 drug–naïve patients with first episode psychosis had been recruited from those presented to the out-patient, causality or in-patient facilities of the Psychological Medicine Hospital. Only 25 were enrolled and completed the protocol. Of the 7 patients who were screened but excluded, 4 were non Kuwaiti, 2 were diagnosed as substance induced psychosis, and one refused to give consent.

- ***Group II (Chronic patients with schizophrenia):***

Twenty Five patients with more than 10 years duration of illness constituted the chronic illness group. They were randomly selected from the chronic in-patient wards. Their duration of illness, and type of antipsychotic drug used- whether typical or atypical- were also mentioned.

Clinical Diagnosis and assessment:

Patients meeting the inclusion criteria were interviewed by one of the research psychiatrists. Diagnostic interviews included: Demographic data for all

patients, their medical and/or psychiatric history, family history, and duration of illness. For the 1st episode psychosis patient group, family members & data providers were strictly asked to determine when exactly (to the nearest week) did they notice any change in the patients' behavior. Patients with noticeable symptoms for more than one month were eliminated from the study.

All participants underwent the structural clinical interview for DSM-IV Axis I disorder (SCID; First et al 1995). Patient's symptoms severity was evaluated with the Positive and Negative Syndrome Scale (PANSS; Kay, el al 1987) and the Clinical Global Impression (CGI; Guy, 1976).

Inclusion criteria for patients:

-Drug-naïve patient experiencing their first-episode psychosis (constituting the first group).

Age 16-50 Years.

Only Kuwaitis were included.

Exclusion criteria:

History of prior use of neuroleptics or ECT treatment, organic or substance – induced psychosis, &/or metallic implants or pacemakers.

Control Subjects:

Forty healthy control subjects were recruited from the radiology department at Ibn Sina hospital - by one of the researchers (radiologist) - after completing a semi-structured sheet & the General Health Questionnaire (Goldbarg 1972). Control subjects were divided into two groups. Twenty healthy control subjects matched the acute patients group, and the other 20 matched the chronic group for age, gender, and education. Exclusion criteria were any Axis I DSM-IV psychiatric disorder, history of substance abuse, history of any gross medical or neurological disorders.

Imaging protocol & volume measurements:

The outline of the temporal lobe was traced on each section, and the outlines of the amygdala and hippocampus were traced on the sections in which they appeared. The posterior boundary of the hippocampus and temporal lobe was set at the level of the last section on which the midbrain collicular plate appeared. For the hippocampus, the choroid fissure was the superior boundary, the inferior temporal horn of the lateral ventricle was the lateral boundary, and the white matter of the para-hippocampal gyrus was the inferior boundary. Anteriorly, the white matter of the alveus delineated the boundary between the hippocampus and amygdala. If the delineation between the amygdala and hippocampus was not seen, the tracing followed the lateral and inferior boundaries to the medial edge of the gray matter; a straight horizontal line then was drawn to the beginning of the trace at the lateral edge. The resulting outlined areas were used to calculate the estimated left and right hippocampal volumes.

Magnetic resonance image acquisition & processing:

MR imaging was obtained using single 1.5-T scanner (Signa horizon, General Electric medical system) Head positioning was standardized using cantho-meatal landmarks, head movement was minimized by foam padding and straps across the forehead & chin. An 8 channel high resolution head coil was used. A 3D volumetric spoiled gradient recalled echo in the steady state sequence generated 60 contiguous 3mm coronal oblique slices

perpendicular to hippocampus TR 9, TE 2, ET 0, matrix 320X256, FOV 24cm & Axial T2 FSE TR 7000 TE 88 ET 25 5mm thick with 1.5 spacing matrix 512X256 FOV 24 cm to exclude organic lesions & other pathologies. Magnetic resonance imaging data were transferred to a workstation (Advantage windows V4.1) and analyzed. Hippocampal volumes were estimated using manual tracing & the above mentioned defined anatomical criteria. One rater performed all hippocampal tracing included in the analyses. One limitation of our study in comparison with previously published article discussing the same subject, we don't correlate hippocampal volume with the whole brain volume, yet advantages of our study are thinner slices perpendicular to hippocampus of the 3D volume acquired & more defined anatomical landmarks.

Statistical methodology:

Data were collected and coded then entered into an IBM compatible computer, using the SPSS version 12 for Windows. Entered data were checked for accuracy then for normality, using Kolmogorov-Smirnov test. Qualitative variables were expressed as number and percentage while quantitative variables were expressed as mean ($\overline{X}$) and standard deviation (S.D.). The arithmetic mean ($\overline{X}$) was used as a measure of central tendency, while the standard deviation (S.D.) was used as a measure of dispersion.

The following statistical tests were used:-

Independent samples t-test was used as a parametric test of significance for comparison between two sample means, after performing the Levene's test for equality of variances.

Independent samples Mann-Whitney's U-test (or Z-test) was used as a nonparametric test of significance for comparison between two sample medians.

The χ^2-test (or likelihood ratio =LLR) was used as a non-parametric test of significance for comparison between the distribution of two qualitative variables.

The Kruskal-Wallis test (χ^2-value) was used as a non-parametric test of significance for one-way comparison between more than two samples means, when the one-way ANOVA test was not appropriate.

The Spearman's rank correlation coefficient (r) was used as a non-parametric measure of the mutual relationship between two not-normally distributed quantitative or ordinal variables.

A 5% level is chosen as a level of significance in all statistical significance tests used.

Results:-

Demographic Data and clinical characteristics:

As shown in table (**1**), there was no significant difference between patients and their age, gender, and education- matched healthy control subjects. It also shows that more than half of patients-either acute or chronic were single, while a large proportion of healthy control subjects were married. The differences in the current marital status between all groups were at a significant level (***p=0.002***).

Nine patients with 1st episode psychosis (*36%*) had family history of mental disorders compared to 15 chronic schizophrenics *(60%)*. Statistical difference between both groups was insignificant (χ^2=***2.89*** & ***p*** value=***0.09***). Five *(20%)*; 4 *(16%)*; 3 *(12%)* & 2 *(8%)* of the studied chronic schizophrenics had family history of schizophrenia; more than one disorder;

epilepsy & mental retardation, respectively, compared to 4 *(16%)* of the 1st episode psychosis patients group who had family history of schizophrenia; 2 (*8%*) had family history of more than one disorder & only one patient *(4%)* reported family history of substance abuse.

Regarding current medical condition & current use of medications, 3 *(12%)* of 1st episode psychosis patients & only 1*(5%)* of their control group have diabetes mellitus & were receiving regular medical treatment. While, 16 *(64%)* of the chronic schizophrenics & only 3 *(15%)* of their control group have diabetes mellitus &/or hypertension & were put on regular medications. Comparison between all groups revealed high significant difference (Likelihood Ratio=***56.3*** & ***p*** value=***0.000***).

Table (**2**) summarizes the clinical characteristics of the 1st episode psychosis and chronic schizophrenia patient groups. As shown in the table, although total scores of **PANSS** (Positive & Negative Symptoms Scale) & **CGI** (Clinical Global Impression scale severity) were higher in 1st episode psychosis patients than in chronic schizophrenics, yet, there were no statistical significant differences between both groups. Patients with 1st episode psychosis tended to have higher PANSS negative symptoms scores, while chronic patients had higher PANSS positive scores. The differences did not rise to a statistically significant level.

Hippocampal volume results:

The volumes of the right and left hippocampi in the four studied groups are shown in table (**3**). The major finding from this table is the significant reduction in hippocampal volumes for both patients groups relative to their control groups (***p=0.000***).

The reduction was more in the left hippocampus than in the right hippocampus in both patient groups, even though the difference between left & right hippocampal volumes was not statistically significant in the four studied groups *(**p > 0.05**)*.

Regarding effect of gender on hippocampus volume measures in all of the 4 groups both on the Rt. & Lt sides, all results were insignificant between Rt. & Lt hippocampus after putting the gender effect (using t-test for equality of means) *(p > 0.05),* except for female chronic schizophrenic patients where their mean Lt. hippocampal volumes (*2329.56 mm³ ± 102.89*) was significantly different than their mean Rt. hippocampal volumes (*2030.55 mm³ ± 304.02*), *(t-value = **2.79** & p = **0.02**)*.

To verify the effect of aging on normal hippocampal volume, we correlated the variable of age to the hippocampal volume in both of the control groups with different means of age (*28.3 ± 8.2* years in control group of 1st episode psychosis patients & *44.5 ± 7.8 years* in control group of chronic schizophrenics) by using ***Spearman's rho technique***, we found no significant correlations between age & hippocampal volumes neither on the right nor on the left hippocampi in both control groups *(**p > 0.05**)*.

After neutralizing the effect of age on normal hippocampal volume, we collected both of the control groups in one ***main control group*** *(n = 40)* then by Post Hoc tests (detailed ANOVA test), we could compare means of hippocampal volumes of the remaining three groups (1st episode

psychosis patients ; chronic schizophrenics & main control group) on both right & left sides. Each couple of these three groups were compared regarding right & left sides. Chronic schizophrenics had the most significant smallest mean hippocampal volumes (*2551.80 ± 492.18 mm³* on the Rt. side & 2518.84 ± *519.58 mm³* on the Lt. side) than 1st episode psychosis patients (*3308.80 ± 465.66 mm³* on the Rt. side & 3175.08 ± *697.27 mm³* on the Lt. side) whose right & left hippocampi were also significantly smaller than right & left hippocampi of the main control group (*3824.55 ± 187.00 mm³* on the Rt. side & 3833.60 ± *266.92 mm³* on the Lt. side) (**MRI images 1-3**). On both right & left sides, the differences were highly statistically significant (*p = **0.000***) Figure (**1**).

Hippocampal volumes in patients receiving either typical or atypical antipsychotic drugs are listed in table (**4**). Chronic schizophrenic patients on atypical antipsychotics had larger Rt. & Lt. mean hippocampal volumes than those on typical antipsychotic drugs. The difference was statistically significant (***p=0.011***) on the left, but, was **marginally** significant (***p=0.052***) on the right side.

Correlation between significant variables inside each of the patients' groups separately:

Table (**5**) demonstrates Spearman's rank correlation coefficient value for the relationship between some of the quantitative significant variables inside **1st episode psychosis patient group**. The results were as follows:-

- The table shows a negative significant correlation between age & score of general psychopathology (of PANSS), and between age and Rt. hippocampal volume.
- Duration of illness did not correlate with either severity of symptoms or the hippocampal volume.
- Total PANSS score was directly correlated to both sub-scores of PANSS and CGI scores. A significant positive relation was found between both the **total** PANSS score as well as score of **negative symptoms** and the Rt. hippocampal volume (p=0.032; p=0.002), respectively, whereas the correlation was significantly negative with the Lt. hippocampal volume (p=0.04; p= 0.03), in order.
- We also found, high significant correlation between scores of CGI & all scores (total & sub-scores) of PANSS in 1st episode psychosis patients (p< 0.01).
- There was no significant correlation between Rt. & Lt. hippocampal volumes in the acute group of patients, but they were directly related in the chronic group (i.e. reduction of the hippocampus in one side was significantly related to the reduction of the other side).

Table (**6**) shows the correlations between some of the quantitative significant variables in **chronic schizophrenic patient group**:-

- Age was directly related with the total severity of symptoms especially the positive symptoms. Age also is inversely related to hippocampal volumes (the more the age, the more reduction in hippocampal volumes in chronic schizophrenics); the correlation was significant on Lt. side but not on Rt. side.

- There were highly significant positive correlations between the total score of PANSS & the severity of the 3 subsets of the sc
- ale as well as CGI score ($p<0.01$).
- Lt. hippocampal volume had a direct correlation with total PANSS score & with the severity of positive symptoms.
- Rt. hippocampus volume was not correlated significantly to any of the parameters employed in chronic schizophrenic group.

Table (1): Socio-demographic data of the four studied groups:-

Variables	1st episode psychosis patients *(n=25)*	Control group of 1st episode patients *(n=20)*	Chronic schizophrenic patients *(n=25)*	Control group of chronic patients *(n=20)*	Values (t / χ^2 / LLR)	p value
Age (*Mean ± SD*)	*29.9 ± 9.1*	*28.3 ± 8.2*	*45.9 ± 8.0*	*44.5 ± 7.8*	t^1 0.64 t^2 0.56	P^1 0.53 P^2 0.58
Gender Male Female	 12 13	 10 10	 16 9	 12 8	1.71	0.64
Current level of education No formal education Primary school Preparatory school Secondary school University	 0 2 5 15 3	 0 2 4 12 2	 4 5 3 9 4	 0 5 3 8 4	16.93	0.15
Marital status Single Married Separated Widowed Divorced	 16 6 3 0 0	 9 10 0 0 1	 16 7 0 0 2	 2 14 2 1 1	31.16	0.002*
Family history of mental disorders Yes No	 9 16	 - -	 15 10	 1 -	2.89	0.09

* Correlation is significant at the 0.05 level

P^1, t^1 = Independent sample t-test &correlation between 1st episode psychosis patients and their control.

P^2, t^2 = Independent sample t-test &correlation between chronic schizophrenic patients and their control.

χ^2 = Chi-square (Kruskal Wallis test).

LLR = Likelihood Ratio.

Table (2): Clinical data of patients with 1st episode psychosis, versus patients with chronic schizophrenia:-

Scales		1st episode psychosis patients *(Mean ± S.D.)*	Chronic schizophrenic patients *(Mean ± S.D.)*	t	p value
PANSS Scores	Total	*92.7 ± 22.5*	*88.1 ± 20.1*	0.76	0.45
	Positive	*20.3 ± 7.2*	*23.9 ± 10.0*	1.44	0.16
	Negative	*27.8 ± 8.2*	*25.4 ± 7.3*	1.13	0.27

	General psychopathology	*44.6 ± 11.5*	*38.9 ± 10.7*	1.81	0.08
Clinical Global Impression Scale severity		*5.7 ± 1.3*	*5.1 ± 1.0*	2.13	0.06

PANSS= Positive & Negative Symptoms Scale

t = t-value (Independent sample t-test)

*** Correlation is significant at the 0.05 level (p value)**

Table (3): Hippocampal volumes (mm^3) in patients with 1st episode psychosis, chronic schizophrenics, & their control groups:-

Group	Rt. Hippocampal Volume			Lt. Hippocampal Volume		
	Mean ± S.D. *(mm^3)*	*t*	*p* value	*Mean ± S.D.* *(mm^3)*	*t*	*p* value
1st episode psychosis patients *(n=25)*	*3308.80 ± 465.66*	4.97	0.000**	*3175.08 ± 697.27*	4.46	0.000**
Control group of 1st episode psychosis patients *(n=20)*	*3826.85 ± 209.02*			*3879.55 ± 332.34*		
Chronic schizophrenic patients *(n=25)*	*2551.80 ± 492.18*	12.06	0.000**	*2518.84 ± 519.58*	11.41	0.000**
Control group of chronic patients *(n=20)*	*3822.25 ± 167.55*			*3787.65 ± 177.07*		

*** * Correlation is significant at the 0.01 level (p value)**
t = t-value (Independent sample t-test)

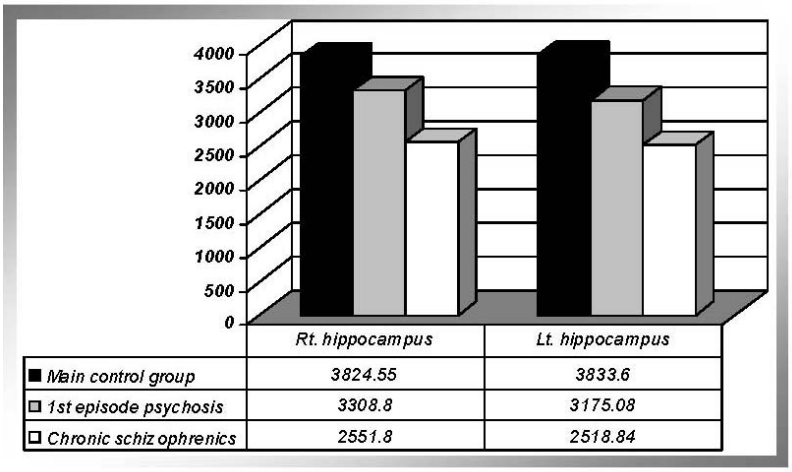
Table (4): Effects of antipsychotics (typical / atypical) on Rt. & Lt. hippocampal volumes, in chronic schizophrenic patients:-

Antipsychotics	Rt. Hippocampal Volume			Lt. Hippocampal Volume		
	Mean ± S.D. *(mm^3)*	*t*	*p* value	*Mean ± S.D.* *(mm^3)*	*t*	*p* value
Typical *(n=9)*	*2357.33 ± 66.66*	2.03	0.052	*2180.78 ± 424.64*	2.75	0.011*
Atypical *(n=16)*	*2661.19 ± 591.41*			*2709.00 ± 478.15*		

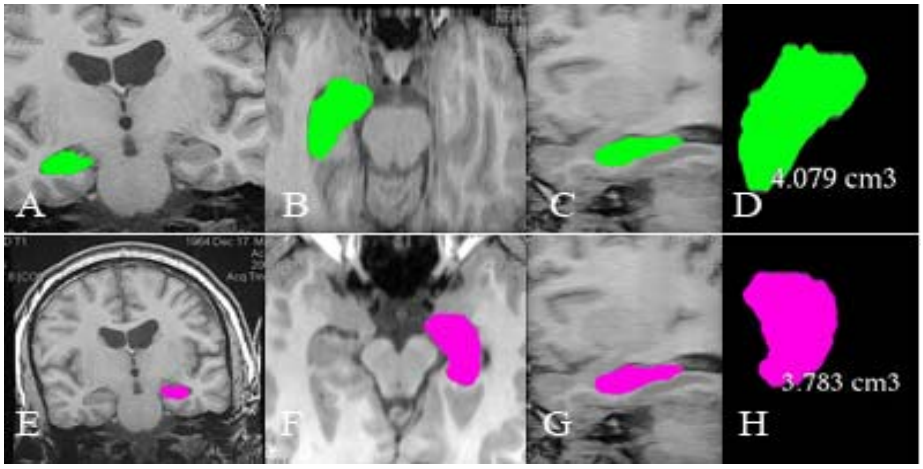
*** Correlation is significant at the 0.05 level (p value)**

t = t-value (Independent sample t-test)

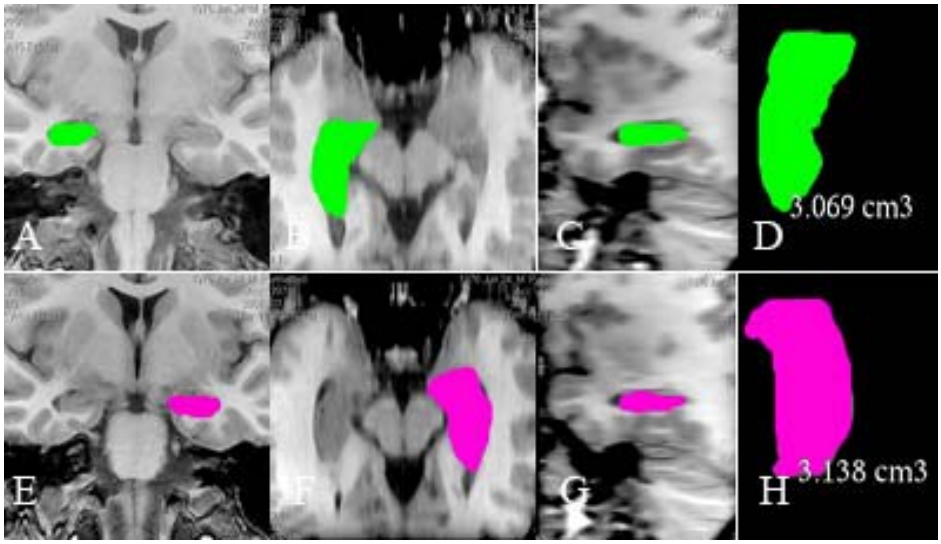
Figure (1): Comparison between Rt. & Lt. hippocampal volumes (*mm^3*) in main control group (*n=40*); 1st episode psychosis patients (*n=25*), & chronic schizophrenics (*n=25*).



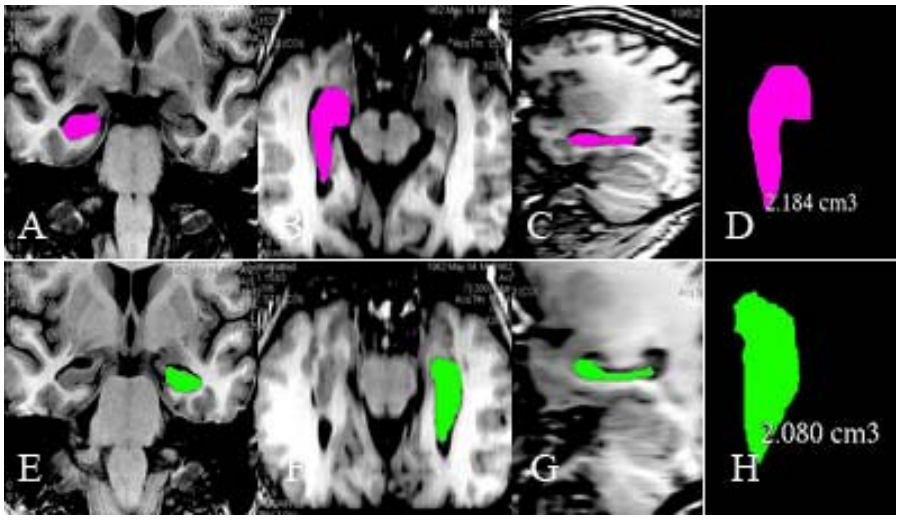
	Rt. hippocampus	Lt. hippocampus
Main control group	3824.55	3833.6
1st episode psychosis	3308.8	3175.08
Chronic schizophrenics	2551.8	2518.84



MRI images (1): <u>Hippocampal volume in a healthy subject</u>. A, B, C & E, F, G are coronal, axial, & sagittal reformatted images from the 3D T1 SPGR. Images of the right side (above) shaded with green & left side (below) shaded with pink. The hippocampus shaded with green & pink, D, & H shows the calculated volume of the hippocampus.



MRI images (2): Hippocampal volume in a 1st episode psychosis patient. A, B, C & E, F, G are coronal, axial, & sagittal reformatted images from the 3D T1 SPGR. Images of the right side (above) shaded with green & left side (below) shaded with pink. The hippocampus shaded with green & pink, D, & H shows the calculated volume of the hippocampus.



MRI images (3): Hippocampal volume in a chronic schizophrenic patient. A, B, C & E, F, G are coronal, axial, & sagittal reformatted images from the 3D T1 SPGR. Images of the right side (above) & left side (below) the hippocampus shaded with green & pink, D, & H shows the calculated volume of the hippocampus.

Table (5): Spearman's rank correlation coefficient value for the relationship between some of the quantitative significant variables inside **1st episode psychosis patient group**:-

Variables	*r–value & p value*	Age	Duration of illness in Days	Total score of PANSS	Score of positive symptoms	Score of negative symptoms	Score of general psycho-pathology	CGI severity	Rt. Hippocampal Volume
Age (years)	*r* *p*								
Duration of illness in Days	*r* *p*	.031 .88							
Total score of PANSS	*r* *p*	.15 .48	-.19 .42						
Score of positive symptoms	*r* *p*	.02 .94	-.08 .70	.84 .000**					
Score of negative symptoms	*r* *p*	.27 .19	-.23 .26	.91 .000**	.81 .000**				
Score of general psychopathology	*r* *p*	-.42 .04*	-.16 .46	.69 .000**	.46 .02*	.51 .01*			
CGI severity	*r* *p*	.06 .77	-.39 .05	.88 .000**	.83 .000**	.75 .000**	.53 .006**		
Rt. Hippocampal Volume	*r* *p*	-.58 .002**	-.05 .83	.43 .03*	.34 .10	.58 .002**	.12 .58	.33 .11	
Lt. Hippocampal Volume	*r* *p*	-.10 .63	-.13 .55	-.49 .04*	-.14 .50	-.43 .03*	-.16 .43	-.09 .67	.24 .24

PANSS = Positive & Negative Symptoms scale CGI = Clinical Global Impression Scale
r = r - value (Spearman's rho test).
*** Correlation is significant at the 0.05 level (p value)**
**** Correlation is highly significant at the 0.01 level**
(-) = negative correlation.

Table (6): Spearman's rank correlation coefficient value for the relationship between some of the quantitative significant variables inside **chronic schizophrenics group**:

Variables	*r–value & p value*	Age	Duration of illness in Years	Total score of PANSS	Score of positive symptoms	Score of negative symptoms	Score of general psycho-pathology	CGI severity	Rt. Hippocampal Volume
Age (years)	*r* *p*								
Duration of illness in Years	*r* *p*	.17 .41							
Total score of PANSS	*r* *p*	.47 .02*	.12 .55						
Score of positive symptoms	*r* *p*	.44 .03*	.48 .01*	.58 .002**					
Score of negative symptoms	*r* *p*	.16 .46	.25 .23	.52 .008**	.34 .10				
Score of general psychopathology	*r* *p*	.35 .09	.31 .12	.87 .000**	.31 .14	.70 .000**			
CGI severity	*r* *p*	.29 .16	.08 .69	.90 .000**	.27 .20	.73 .000**	.83 .000**		
Rt. Hippocampal Volume	*r* *p*	-.35 .08	-.05 .81	.30 .14	.31 .13	-.06 .76	.29 .17	.28 .17	
Lt. Hippocampal Volume	*r* *p*	-.52 .007*	-.24 .25	.39 .04*	.58 .003**	-.26 .21	.04 .85	.23 .27	.68 .000**

PANSS = Positive & Negative Symptoms scale
CGI = Clinical Global Impression Scale
r = r - value (Spearman's rho test).
*** Correlation is significant at the 0.05 level (p value)**
**** Correlation is highly significant at the 0.01 level**
(-) = negative correlation.

Discussion:

Reviews of MRI studies in schizophrenia consistently find reduction in hippocampal volume in patients compared with controls ***(Szeszko et al 2003; Wright et al., 2000; Whitworth et al 1998).*** This is true regarding the current study, where bilateral volume reduction of hippocampi was greater in both the acute and chronic patient groups than in control groups, with more reduction in chronic schizophrenic patients relative to drug- naïve patients in their acute stage.

While the above conclusion is supported by many studies such as ***Chakos et al.; 2005; Velakoulis et al 1999***, others didn't support such findings. ***Delisi et al. 1991*** found no difference in brain volume at illness onset; his findings were parallel to the conclusion of ***Gur et al 1998*** - in his longitudinal prospective study - who didn't find differences in volume reduction between first episode patients and chronic schizophrenics as compared to controls. The differences in findings between studies

were mainly explained by methodological difficulties with thick MRI slices.

The previous results raise a question, if structural hippocampal changes are neuro-developmental or neurotoxic in nature?

In the current study, the presence of bilateral hippocampal volume reduction and more severe illness in first episode psychosis group of patients could suggest a genetic risk (neuro-developmental), while more reduction in chronic group may support illness neurotoxic effect. The hippocampal volume reduction was not related to duration of illness in both patient groups. Our conclusion coincides with that of ***Chakos et al 2005; John et al. 2002***; & ***Nelson et al 1998***. Many other studies support the hypothesis of genetic vulnerability e.g. ***Csernansky et al 2002***, who concluded that abnormalities in shape and asymmetry were present at onset but was not correlated with either severity or duration of illness, findings suggestive of genetic risk. Also, ***Beng Choon Ho et al 2005*** reported that hippocampal morphology and volume were not associated with duration of untreated initial psychosis, supporting the neuro-developmental hypothesis. ***Velakouilis et al 1999*** reported that left sided volume reduction was present in both groups (acute and chronic), while right side volume reduction increased with chronicity which raised two possibilities either right sided specificity for chronicity or volume reduction is more likely to have chronic course.

The current results may also support the neurotoxic hypothesis, where patients with chronic schizophrenia- in spite of being treated and have less severe psychosis - had smaller hippocampal volumes than patients in their first episode psychosis. The neurotoxic hypothesis was supported by some studies (Leiberman 1999; Delisi 1997; Miller 1989) denoting the illness effect with time.

The neurotoxic hypothesis may be true if the degree of volume reduction was correlated with variables such as chronicity, treatment variable, psychopathological severity and socio-demographic data as well as clinical variables.

Regarding age effect: In the present study, age was negatively related to the hippocampal volume in the left but not the right hippocampus. The same was reported by ***Velakoulis et al 1999***. In our findings, the age has only a differential effect being directly related to the reduction in the volume of the right hippocampus in the acute group, and to the left hippocampal volume reduction in the chronic group. This differential effect was supported by the findings of ***Chakos et al. 2005; & Seidman et al 2002.***

Gender also had a differential effect on chronic schizophrenic patients but not on acute group, were female patients were significantly associated with more left hippocampal volume reduction. This may suggest high vulnerability of female patients to structural brain changes with chronicity. The differential effect of gender was also reported by ***Szeszko et al 2003 & Szeszko et al 2002*** while no gender effect was reported by ***Velakoulis et al 1999***.

An interesting finding in the current study was that chronic schizophrenic patients on atypical antipsychotics had larger Rt. & Lt. mean hippocampal volumes than those on typical antipsychotic drugs. A finding which may suggest that patients treated with atypical antipsychotics may lose less hippocampal tissue if given such treatment

early after illness onset. Similar findings were reported by ***Chakos et al. 2005; & Lieberman et al 2005*** who assessed brain volume changes in first episode psychosis, haloperidol treated patients had significant reductions in gray matter volume, whereas Olanzapine group had not. There was no correlation between dose and brain volume changes. Preclinical studies have suggested that atypical antipsychotics could have a neurotrophic or a neuroprotective effects ***(Halim et al 2004; Bai et al 2003).***

What is unique in our result is the differential effect for the PANSS subscales. First episode patients with more severe negative symptoms had smaller left but not right hippocampi. Similar result was reported by ***Sigmundsson et al 2001***.Moreover; patients with high positive symptoms score had smaller left hippocampi volume in chronic patients. The above two findings may indicate specificity of left sided hippocampus for differential illness severity effect.

From above we can conclude that illness severity may have differential effect on hippocampal volume rather than illness duration. In contrast to ***Hohn et al. 2002*** who did not find a significant relation between illness severity and hippocampal shape and asymmetry.

Lack of effect of illness duration on hippocampal volume with differential effect of age, gender and severity may suggest neuro-developmental hypothesis, while volume reduction in chronic group indicate that neurotoxic effect hypothesis is there to some extent. But still we can not conclude that these volumetric changes are specific to schizophrenia. The same suggestion was mentioned by ***Colter and Parianto 2002*** that brain changes found at onset or possibly after are not purely developmental and not specific for schizophrenia.

Conclusion & Recommendations:

- Bilateral hippocampal volume reduction was present in chronic more than acute patients and in both groups of patients than in control groups.
- Both neuro-developmental and neurotoxic hypothesis could be suggested. More longitudinal prospective studies are needed.
- Hippocampal reduction was not related to duration of illness.
- Age, gender and illness severity have differential effect on the volume of the right and left hippocampai.
- Atypical antipsychotic may have positive effect on hippocampal volume suggesting a neuroprotective effect and favoring early treatment. This conclusion can not be generalized, because of the small sample size &/or the hippocampal volume could be affected by other combinations of different psychotropic drugs used by chronic patients during their past years of illness.

This speculation needs prospective longitudinal study and more sophisticated techniques as well as big size sample of patients, and normal healthy control.

Limitations:

1. The current study lack a sample size sufficient to test genetic &/or neurotoxic hypotheses.
2. In spite of being a cross-sectional study, as we did not follow–up the acute patient group to know their final diagnosis, yet, a significant bilateral

reduction of the hippocampi was detected during this early stage of illness. This may suggest a relation between hippocampal reduction and the development of psychosis in general, but not specifically for schizophrenia.

3. We couldn't adjust the hippocampal volume with the whole brain volume because of technical difficulties.

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حجم الجسم الفرسي عند مرضى الفصام المزمن ومرضى نوبة الذهان الأولي

يعتبر صغر حجم الجسم الفرسي من التغيرات التركيبية المتواترة في مرضى الفصاميين وترجع هذه التغيرات اما لأحداث جينية وتكوينيه سابقة للمرض أو ناتجة عن المرض ذاته . دراسة حجم الجسم الفرسي عند عينة من مرضى الفصام المزمن ومرضى ممّن يعانون نوبة الذهان الأولي . تمت دراسة حجم الجسم الفرسي عن طريق أشعة الرنين المغناطيسي في ٢٥ من المرضى الذين يعانون مرض الفصام لمدة أكثر من عشر سنوات وكذلك في ٢٥ مريض يعانون نوبة الذهان الأولي ولا يتناولون مضادات الذهان. تم تشخيص الحالات عن طريق المقابلة المقننة للتقسيم الأمريكي الرابع للأمراض النفسية . أختير عدد ٤٥ فرد من أناس لا يعانون من أي أمراض أو أعراض نفسية حالية بعد خضوعهم إلى إختبار مقياس الصحة العامة وتم قياس حجم الجسم الفرسي عندهم كعينة ضابطة . تم دراسة بعض العوامل الشخصية والإكلينيكية المختلفة ومدى ارتباطها وعلاقتها بالتغيرات الحادثه في حجم الجسم الفرسي عند كلا المجموعتين . وجد أن حجم الجسم الفرسي لكلٍ من مرضى الفصام المزمن وكذلك مرضى الذهان أصغر منه في الأفراد بالعينه الضابطة .وجد أيضاً أن حجم الجسم الفرسي عند مرضى الفصام المزمن أصغر منه عند مجموعة المرضى اللذين يعانون الذهان لأول مرة . أظهرت الدراسة عدم ارتباط مدة المرض بصغر حجم الجسم الفرسي. هناك تأثير مختلف للعوامل الشخصية والإكلينيكية الأخرى على حجم الجسم الفرسي في كلتا الناحيتين اليمنى واليسرى . وجد أن حجم الجسم الفرسي أكبر إلى حد ما في مجموعة أفراد الذهان المزمن ممن يتناولون أدويه من الجيل الثاني لمضادات الذهان عن من يتناولون أدويه من الجيل الأول . تظهر النتائج أن كلٌ من فرضية العامل الجيني والتركيبي ما قبل المرض وكذلك تأثير المرض ذاته على صغر حجم الجسم الفرسى موجودة وقابلة للتحقق.نحتاج إلى رؤية أكثر وضوحاً لتأثير الذهان على حجم الجسم الفرسي ومدى علاقته السببية للمرض عن طريق دراسة طويلة ومتتابعة على مدى فترة زمنية أطول وبحجم عينة أكبر من المرضى مع توافر تكنولوجيا ذات تقنية عالية .