Duration of Illness and Treatment Effects on Hippocampal Volume in Male Patients with Schizophrenia

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ABSTRACT

Background Volume reduction of the hippocampus is one of the most consistently described structural abnormalities in patients with schizophrenia. However, the cause and timing of this pathomorphologic feature of the illness is not known.

Aims To examine the relationship of duration of illness and treatment effects on hippocampal volumes in male patients with schizophrenia or schizophreniform disorder.

Method Quantitative 1.5 Tesla MRI examinations of the brain were obtained on a young male patient group in the early stage of illness and an older group of male schizophrenic patients who were chronically ill. MRI examinations of the brain were also acquired for right-handed male controls matched to both patient groups for age and handedness. Patients were characterized with regards to duration of illness and illness severity utilizing PANSS assessments.

Results Patients had smaller hippocampal volumes than controls. The volume reduction was larger for the older patients than for the young patients as compared to their age-matched controls. Within the early illness group of patients, treatment with atypical antipsychotic medication rather than haloperidol was associated with larger hippocampal volumes even after controlling for differences in illness severity.

Conclusions The greater reduction of hippocampal volume in chronic patients vs early illness patients compared to their respective controls, and after controlling for illness severity and age, supports the hypothesis of progressive hippocampal reduction in male schizophrenic patients. Treatment with atypical antipsychotic medication early in illness may protect against hippocampal volume reduction in male schizophrenic patients.

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INTRODUCTION

Reviews of structural magnetic resonance imaging (MRI) studies in schizophrenia consistently find reduction in hippocampal volume in patients compared to control subjects (Wright et al 2000). The magnitude of volumetric decreases is usually less than 10% (0.5cc) of the total absolute volume in a given sample. These reductions in hippocampal volume may be a consequence of neurodevelopmental events which preceded the onset of the illness, or there may be further reductions that occur after illness onset. In a cross-sectional study, Velakoulis et al (1999) reported left hippocampal volumes reductions in both treatment naïve first episode and chronic schizophrenic patients, but right hippocampal volumes reductions only in chronic patients. This finding suggests that there are further reductions in hippocampal volumes after illness onset. The study was limited by its failure to use both young and old control groups who were matched to first episode and chronic patient groups for age and gender.

METHODS

The current study is cross-sectional in design and assesses potential differences in the volume of the hippocampus between patients in the first few years of illness vs. patients who have been chronically ill. The study design is unique in that we have matched early illness patients to a young control group and chronic patients to an older control group. We have also eliminated the confounding effects of gender and handedness by studying only right-handed males. Patient and control subjects were excluded for any clinically significant neurological or medical disorder, a history of head trauma with loss of consciousness, current substance abuse, a lifetime history of substance dependence, or use of designer drug on more than two occasions.

Our apriori hypotheses were that male patients would have smaller hippocampal volumes than controls and that the patient-control difference would be greater for the chronically ill patients than for the patients in the first few years of illness. In addition, as an exploratory analysis we examined the effects of duration of illness on hippocampus volume after controlling for age, severity of illness and intra-cranial cavity (ICC) in both the young and older patient groups. Possible causes for different patterns in the two groups were explored, including the effect of antipsychotic medications.

Subjects. Ninety-three right-handed male patients who met DSM-IV criteria for schizophrenia or schizophreniform disorder were recruited from UNC Hospitals and Duke University Medical Center from August 1997 to July 1999. Subjects 16-30 years of age with less than 5 years total duration of illness defined an early phase of illness study group (N=34) while subjects 31-60 years of age with greater than 10 years duration of illness defined a second group of chronic patients (N=22). A total of 93 patients were screened and 56 patients were enrolled and completed the protocol. Of the 37 patients who were screened but excluded, 25 had an inappropriate diagnosis, 6 withdrew consent, and 6 had motion artifact on their scans). Several of the early illness subjects were also participating in a randomized clinical trial comparing haloperidol to olanzapine (Lieberman et al 2003). Subjects underwent a medical screening, the Edinburgh handedness inventory to select right-handed subjects (Oldfield et al 1971), and a

Structured Clinical Interview for DSM IV Axis I Clinical Disorders (SCID; First et al 1995).

Fourteen right-handed male comparison subjects who had a similar age range to the early illness patients and 12 right-handed male comparison subjects who had a similar age range to the chronic patients were also recruited. Controls were excluded for any Axis I DSM-IV psychiatric disorder and for lifetime history of substance abuse or dependence using a SCID interview. Patients were evaluated with the scale for the Positive and Negative Symptoms Scale..

Since this was a cross-sectional study that was not designed to prospectively determine duration of illness in prodromal subjects, duration of first psychotic episode was defined as time when subjects met criteria for schizophrenia. This was determined by thorough chart review, patient and family interview and discussion with the patient's treating physician. .

MRI Protocol and Data Analysis. Patients were scanned on a GE Sigma Advantage MR system operating at 1.5 Tesla and capable of performing MRI/MRS studies. The series used for this study was acquired as a 3D IR Prepped Axial Spoiled Gradient; Fast SPGR Axial plane, 3D Acquisition TE min full; TR=15 ms; flip angle=20 degrees; FOV=24cm; Bandwidth=16KHZ (125Hz/pixel) 256×256×124 slices; 1.5 mm thick slice, 1 NEX. All images were stored on an optical disk and coded into a series number.

Hippocampal Segmentation. Analysis of the hippocampus was performed on a Sun Microsystems workstation utilizing a three-dimensional software package IRIS (University of North Carolina). Hippocampal segmentations included the hippocampus proper, the subiculum, the fimbria, and subsplenial gyrus (figure 1). We utilized the sagittal plane to separate the hippocampus from the amygdala, using the alveus and/or the uncal recess of the temporal horn to separate the structures. More medially in the saggital plane, the axial view was utilized at the level of the tubera cinerium, mamillary bodies, and optic tracts. This corresponds to the level of the hippocampal-amygdala transition area (HATA) in the axial plane. HATA was used as the boundary between the hippocampus and amygdala in the axial plane, which corresponds to the superior-medial boundary of the structure as viewed in the coronal plane (Convitt et al 1999).

The hippocampal body was outlined in the coronal plane from the inferior-lateral border to medial, with the contour following (and thus excluding) the parahippocampal gyrus. The medial border was arbitrarily defined by extending a straight line from the most inferior portion of the hippocampal body at a 45° medial upwardly inclining angle to the superior-medial border of the hippocampus. The anterior boundary was the anterior convexity of the hippocampal alveus, which was previously delineated in the sagittal plane. The superior hippocampal border was the alveus. The inferior border continued to be the parahippocampal region, while the lateral border was the temporal horn of the lateral ventricle or temporal stem.

(Figure 1)

Segmentation of the intracranial cavity. Analysis of the intracranial cavity volume was performed on a SUN Microsystems workstation and were processed using MRX software, developed by GE (Schenectady, NY) in collaboration with Brigham's & Women's Hospital and Duke University Medical Center. This software can employ the contrasts from both images of a dual echo set (proton density and T2 weighted images) to segment tissue types. The details of this method of tissue segmentation have been

previously described (Kikinis et al 1992). After segmentation, a mask corresponding to the intracranial cavity was developed from the segmented images, which allowed elimination of those non-brain tissues from the images. After disconnecting the brain from the extra-axial structures, brain tissue in each slice was highlighted, allowing computation of total intracranial cavity volume, which was the sum of gray and white matter and both intracerebral and extracerebral CSF.

All measurements were completed by a single rater (S.A.S.). The reliability series consisted of 15 scans, 3 from each of a total of 5 subjects. The series were then put in a random order before being evaluated by S.A.S., who was blinded with respect to diagnosis, and were measured within a four month time interval. Intra-rater reliability was 0.86 for the left hippocampus and 0.88 for the right hippocampus. Intra-rater reliability for the intra-cranial cavity was 0.99.

Statistical Analysis. The analyses described herein had two principal objectives: (1) to determine whether patients had smaller hippocampal volumes than controls and whether the control-patient difference increased with age and (2) to explore the effects of duration of illness (DI) on hippocampal volumes in both the patient subgroups after controlling for the effects of age and symptom severity.

To achieve the first objective, a mixed model was utilized to compare each patient group with its corresponding age-matched control group and determine whether the patient-control difference increased with age. The analysis controlled for intra-cranial cavity (ICC) volume by including ICC as a covariate in the model. The left and right hippocampal volumes were treated as repeated measures in order to address the high correlation between the two. Model-based estimates for the sizes of patient-control differences were compared between the young and older groups.

To achieve the second objective, two separate mixed models were performed for the young and older patient groups to assess the association of duration of illness with hippocampal volume in patients while controlling for the effects of age and illness severity. Again, individual ICC volume was adjusted by the model as a covariate, and left and right hippocampal volumes were treated as repeated measures from an individual.

A third set of analyses examined the effects of type of antipsychotic treatment on hippocampal volumes. Since this was a cross-sectional study and most chronic patients had long histories of treatment with both typical and atypical antipsychotic medications, we decided that we could best address the issue of differential drug treatment effects on hippocampal volume in the early illness group. However we examined potential drug effects in both the early illness and chronic patient groups using mixed model analyses in each group. In these analyses the possibility of differential drug effects were examined by utilizing antipsychotic drug type (atypical vs. typical) as a between subject factor, hemisphere as repeated measure, and age, duration of illness, illness severity (PANSS total) and intracranial cavity volume as covariates.

Data were not transformed in the second and third set of analyses, since the distribution of the ANOVA-type of residuals of the outcome variable, hippocampal volume, was normally distributed. Distribution of duration of illness (DI) was skewed, but DI was a continuous variable that was included in the model as a covariate and did not need to be normally distributed. More importantly, we believe that the DI in their original scale is clinically more meaningful. The patients with longer DI in each group are as informative as patients with shorter DI to the study

question we are pursuing. Given the fair number of cases with longer DI, we are convinced that our findings are reliable, and not due to the influence of outliers.

RESULTS

Comparison of Patients and Control Subjects. There was no difference in the mean age of patient subgroups and their respective gender matched comparison subjects: the mean (SD) age (years) for patients in the early phase of illness group and their controls was 21.9(3.9) and 22.7 (2.8) respectively; the mean (SD) for chronic patient group and their controls was 42.8 (8.6) and 41.1 (7.3) respectively. With respect to racial composition, 62% of the early illness patient group, 50 % of the chronic patient group, 86% of the early illness comparison subjects and 58 % of the chronic comparison subjects were Caucasian, and the remainder of the subjects were non-Caucasian (primarily African American). There was no significant difference in racial composition between the four groups ($p = 0.18$ by Fisher's exact test). The subject groups also had comparable social economic status (SES), as measured by the amount of parental education ($p=0.29$ by Fisher's exact test). For each the four groups, the majority of the subjects (>75%) had at least one of their parents with high school or higher education.

Table 1 summarizes the clinical characteristics of the early illness and chronic illness patient groups. Ten of the 34 early illness patients had a diagnosis of schizophreniform disorder and 24 had a diagnosis of schizophrenia. As anticipated, the chronic patient group was older, with longer duration of illness and more hospitalization as compared to the early illness group, as this was part of the study design. However they did not differ on mean measures of clinical psychopathology such as mean PANSS and CGI scores or age of onset. At the time of scan, 17 early illness patients were on typical antipsychotic medication (all of them haloperidol), and 15 were on atypical antipsychotic medications (12 olanzapine, 3 on risperidone), 1 received both typical and atypical antipsychotic medications (clozapine and molindone), and 1 participated in a double clinical trial with antipsychotic medication unknown. For chronic patients, only 5 were on typical medications (3 haloperidol, 1 trifluperazine and 1 thiothixene), and 17 were on atypical medications (6 olanzapine, 8 clozapine and 3 risperidone).

[Table 1]

The absolute volumes of left and right hippocampi for early illness patients, chronic patients and controls are described in Table 2.

[Table 2]

In analysis I, right hippocampal volumes were found to be greater than left hippocampal volumes for both patients and controls [(vol. Diff. 0.12 (0.03) cc, $F_{1,78} = 18.83$, $p=0.001$]. There was a significant association of intracranial volume with hippocampal volume ($F_{1,75}=21.37$, $p=0.001$). The partial correlation of ICC to hippocampal volume after adjusting for age was $r=0.52$ ($p<0.001$).

The major finding from analysis I was the significant reduction in hippocampal volumes for both patient groups relative to their respective control groups [$F_{1,75}=9.1$, $p=0.0034$]. The group by side interaction was not significant. Moreover, numerically,

the amount of reduction was greater in the chronic patients than the early illness patients, even though the difference was not statistically significant. The model-estimated reduction was 0.16(0.09) cc (t_{75}=1.76, p=0.08), or 5.5%, in the early illness group as compared to 0.26(0.10) cc (t_{75}=2.54, p=0.01), or 8.8%, in the chronic illness group. The corresponding effect sizes were "medium", d=0.55, in the early illness group; and "large", d=0.88, in the chronic group (Cohen, 1988).

The results were the same when the analyses were repeated after removing the ten patients within the early illness group who had a diagnosis of schizophreniform disorder rather than schizophrenia.

Effect of duration of illness on hippocampal volumes within the patient subgroups. The strength of this study design was the inclusion of the healthy control groups matched with patient groups in major demographic characteristics. Therefore, separate mixed models were utilized to examine the effects of duration of illness on hippocampal volumes in early illness and chronic patient groups controlling for age and ICC. In the early illness group, patients with longer illness duration had *larger* hippocampal volumes (t_{42}=2.25, p=0.03; partial correlation of hippocampal volume with duration of illness in early group: r=0.38, N = 29, p = 0.03), whereas there was a non-significant association of longer duration of illness with smaller hippocampal volume within the chronically ill group (t_{42}= -0.46, p=0.65). The other analysis controlling for symptom severity (PANSS total) in addition derived very similar results for duration of illness, and the symptom severity effect was non-significant (p>.50 for either group).

Effect of Illness Duration and Type of Antipsychotic in the Early Illness Group. The numbers of early illness patients on typical and atypical antipsychotic drugs, as well as their demographic and clinical characteristics, were listed in table 3. The atypical group was older, with more Caucasians and milder in symptom severity measured by PANSS total, PANSS negative and CGI, but with similar age of onset and duration of illness.

[Table 3]

After controlling for age, ICC and symptom severity (PANSS total), there was a main effect of drug type ($F_{1,26}$= 7.19;p =0.01) within the early illness group, with patients who had been treated with atypical antipsychotics prior to assessment having larger hippocampal volumes than those treated with typical antipsychotics [mean absolute hippocampal volume atypical antipsychotics = 5.81(0.51) cc; mean absolute hippocampal volume typical antipsychotics 5.10(0.52) cc; Figure 2].

[Figure 2]

There was also an interaction between drug type and duration of illness in the early illness group ($F_{1,26}$=6.03; p=0.02). Post-hoc tests indicated that patients with longer duration of illness who were treated with atypical antipsychotic medication had larger hippocampal volumes (t_{26}=3.02, p<.01; correlation of hippocampal volume and duration of illness for early illness patients on atypical antipsychotics adjusted for age, severity of illness and intracranial cavity volume: r=0.61, N=17, p=0.02). There was no association of illness duration with hippocampal volume size in patients treated with typical antipsychotics (t_{27} = -1.02, p=0.32; correlation of hippocampal volume and duration of

illness for early illness patients on typical antipsychotic adjusted for age and intracranial cavity volume: r = - 0.21, N = 17, p=0.45). The analyses were repeated controlling for the effects of race, positive symptoms and negative symptoms and there was no effect of these factors on hippocampal volume, so they were dropped in the final model

Within the chronic patient group there was no association of hippocampal volume with drug type ($F_{1,9}$=0.54, p=0.48) or duration of treatment ($F_{1,9}$ =0.08, p=0.78) and no interaction between drug type and duration of illness ($F_{1,9}$=0.00, p=0.95).

DISCUSSION

Our study found that right handed male patients with schizophrenia had smaller hippocampal volumes than did matched comparison subjects, even after adjusting for the effects of age, hemisphere and intracranial volume. The finding of decreased hippocampal volume in patients is in accordance with the majority of previous reports of studies that examined hippocampal volume in schizophrenia as assessed by structural MRI (Velakoulis et al 1999, Wright et al 2000). In addition, we found that the volume differences between patients and controls were greater in chronic patients, which is consistent findings of Velakoulis et al (1999), as well as a previous report by our group of greater volume reduction in chronic patients compared to first episode and controls (Bogerts et al 1993). The greater reduction of hippocampal volumes in the chronic patient-control comparison than in the early illness patient-control comparison was confirmed utilizing effect size analysis, which measures the magnitude of the effect independent of sample size. Using Cohen's criteria, the effect sizes were "medium", d=0.55, in the early illness patient-control hippocampal volume difference; and "large", d=0.88, in the chronic patient-control comparison (Cohen, 1998).

One possible explanation for the smaller hippocampal volumes in chronic patients than early illness patients is that there are progressive changes in the hippocampi of male schizophrenia patients over the course of illness. Alternatively, our chronic patients could represent a more severely ill subgroup than early illness patients that are over represented in the chronic patient populations. However, we compared the early illness and chronic patients with respect to commonly accepted measures of illness severity (PANSS total and negative and positive subscale scores, CGI scores and age of illness onset) and found no difference in illness severity between the early illness and chronically ill schizophrenic patients. This led us to conclude that the finding of increased hippocampal volume reduction in chronic patients was due to progressive changes in the hippocampus over the course of the illness.

In our analysis of the association of illness duration and hippocampal volume within the patient subgroups, we found that, within the chronically ill group, there was no association of hippocampal volume with illness duration. This suggests that the volume reductions were progressive but not linear, perhaps occurring within the first ten years of the illness. There was an unanticipated association of larger hippocampal volumes with longer duration of illness in the early illness group, which is not consistent with a hypothesis of progressive illness related changes. This led us to consider the possibility that a treatment effect was confounded with illness duration in the early illness group. In examining the differential effect of type of antipsychotic medication and illness duration on hippocampal volume within the early illness group, we found that treatment with

atypical antipsychotics (olanzapine and risperidone) was associated with larger hippocampal volumes than was treatment with haloperidol, after controlling for differences in age and illness severity. Since assignment of drug treatment of early illness patients to haloperidol or atypical antipsychotic medication was randomized in the context of clinical trials that patients were participating in, there was no association with drug class and type of patient. This suggests that male schizophrenic patients treated with atypical antipsychotics early in illness lose less hippocampal volume than those treated with haloperidol.

There are several possible mechanisms by which such potential effects of atypical antipsychotic drugs on the hippocampal volume of patients in the first 5 years of illness could be mediated. Recent studies have shown that neurogenesis of hippocampal cells can continue into adult life (Kempermann et al 2000, Erickson et al 1998). Thus, it is possible that patients with schizophrenia lack or have diminished capacity to regenerate cells over time in adolescence and adulthood. In this context, atypical antipsychotic drugs may stimulate pathways involved in supporting cellular plasticity and resilience as has been demonstrated with mood stabilizing and antidepressant drugs (Santarelli et al 2003). Unlike antidepressants, which increase hippocampal neuronal survival and differentiation in response to stress in part by increasing brain derived neurotrophic factor (BDNF; Malberg et al 2000), both typical and atypical antipsychotics reduce BDNF in the rat hippocampus (Lipska et al 2001). However, antipsychotics have been reported to increase another neurotrophic factor, Bcl-2, an inhibitory protein of apoptosis, in the temporal lobes of schizophrenic patients (Jarskog et al 2000). Perhaps atypical antipsychotic medications exert a neuroprotective effect by upregulating Bcl-2 in the hippocampi of young schizophrenic males.

Atypical antipsychotic medications also modulate glutamatergic activity in the hippocampus. Olney and Farber (1995) proposed that reduced NMDA receptor function in schizophrenic patients resulted in a disinhibition of glutamate in specific corticolimbic circuits, with resulted in neurotoxic effects. Atypical antipsychotic drugs can antagonize the effects of NMDA antagonists, such as ketamine, in the hippocampus (Duncan et al 2000), and may protect against excitotoxic damage in the hippocampus early in the course of illness.

CLINICAL IMPLICATIONS

- In healthy male schizophrenic patients, without history of substance dependence or current substance abuse, there are hippocampal volume reductions compared to age and gender matched controls.
- There are greater reductions in hippocampal volumes of chronic male patients than in early illness patients compared to their respective controls, even after controlling for age and illness severity. This suggests a progressive hippocampal volume reduction during the course of the illness in male patients
- Treatment with atypical antipsychotic medication early in the course of illness may protect against hippocampal reduction in male schizophrenic patients. These potential treatment effects require further study.

LIMITATIONS

- The cross sectional design of this study is less able to address the issue of progressive hippocampal atrophy and treatment effects than a prospective longitudinal study would be.
- The cross-sectional design did not permit us to accurately separate out treated vs. untreated duration of illness. Therefore, we could not examine the effects of duration of treatment on hippocampal volume.
- The assignment to treatment with typical and atypical antipsychotic medications was not random in the chronic patient group.
- With respect to the early illness group many of the subjects were in a randomized clinical trial as well as willing to undergo a brain scan. This may limit the generalizability of the result.
- Our findings are restricted to male subjects without significant substance abuse histories and can not be generalized to female or substance abusing patients.

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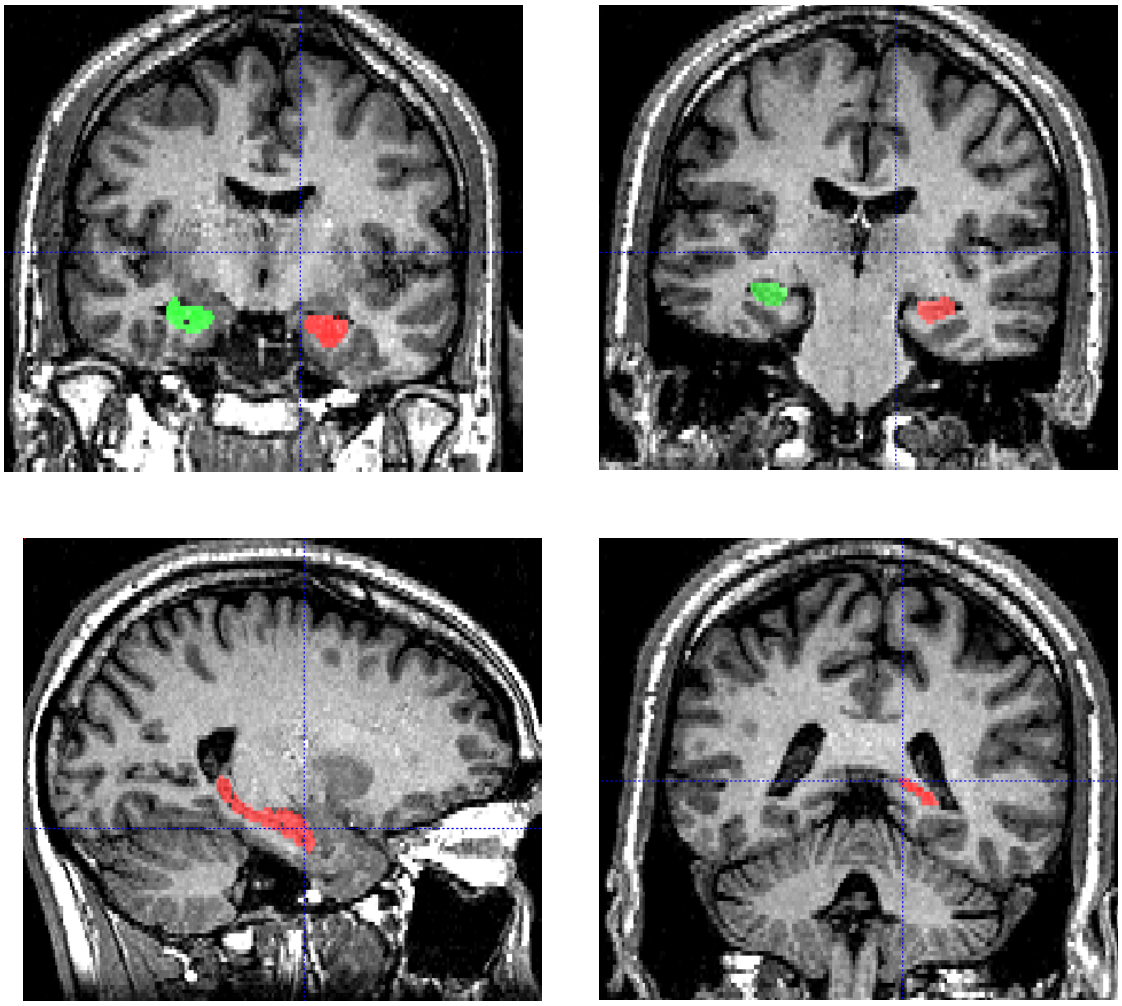
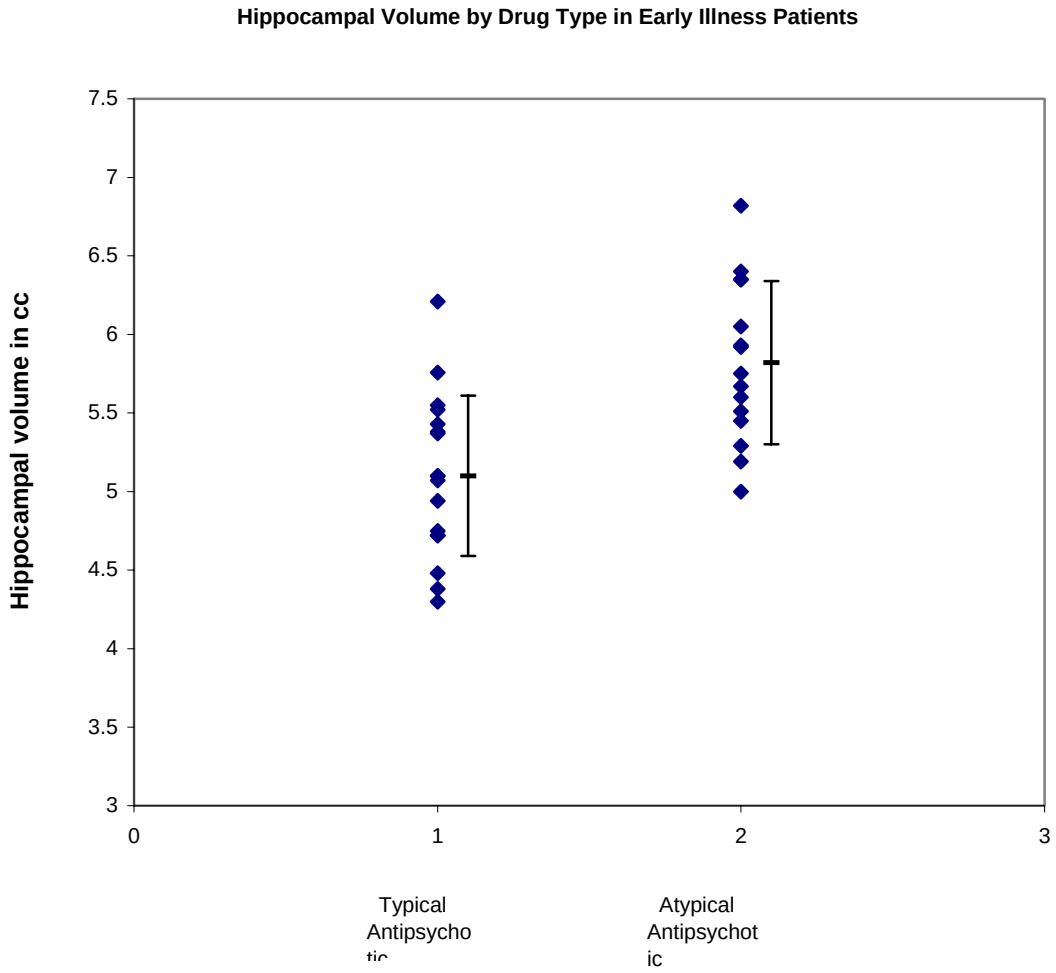
Figure 1




Hippocampal Volume by Drug Type in Early Illness Patients
Hippocampal volume in cc
7.5
7
6.5
6
5.5
5
4.5
4
3.5
3
0
1
2
3
Typical Antipsychotic
Atypical Antipsychotic

Relationship of Hippocampal Volume and Duration of Illness by Drug Type in Early Illness Patients

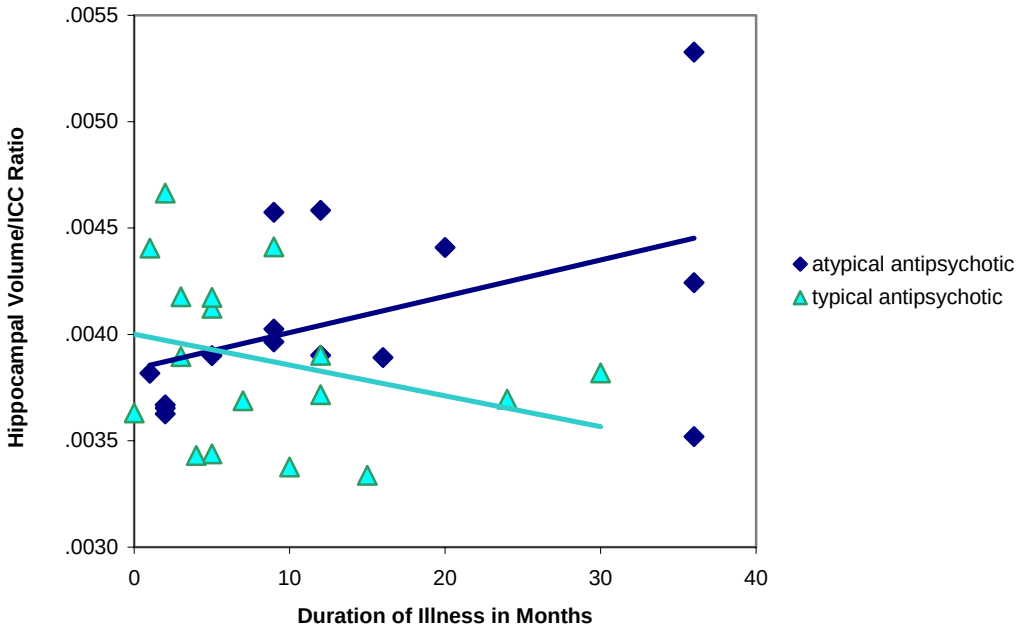


Table 1: Clinical Characteristics of Early Illness and Chronic Patients

	Early Illness Patients (N=34) Mean (SD)	Chronic Schizophrenic Patients (N=22) Mean (SD)
Age at Study entry	24.9 (8.8)	37.1 (11.8)
Duration of Illness (months)	12.41 (11.8)	250.43 (101.06)
Age of Illness Onset	21.14 (4.03)	21.78 (3.8)
PANSS Total	78.55 (21.17)	86.27 (22.83)
PANSS Positive Sub-scale	19.97 (5.25)	22.1 (6.9)
PANSS Negative Sub-scale	19.63 (6.96)	22.1 (6.9)
CGI	4.14 (0.92)	4.5 (1.15)
Drug type when Scanned	Typical Antipsychotic: N = 15 Atypical Antipsychotic: N=17 Both: N=1, Unknown: N=1	Typical Antipsychotic: N=7 Atypical Antipsychotic: N=15

Table 2. Absolute Hippocampal Volumes (cc)

	Early Illness (N=34)		Early Comparison (N=14)		Chronic Schizophrenia (N=22)		Chronic Comparison (N=12)	
Region	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Total ICC	1388.5	159.7	1457.7	109.3	1284.3	139.7	1364.5	117.2
Left Hippocampus	2.66	0.33	2.90	0.31	2.56	0.24	2.88	0.26
Right Hippocampus	2.82	0.43	3.07	0.38	2.61	0.34	3.01	0.30

Table 3: Clinical Characteristics of Early Illness Patients on Typical and Atypical

	Typical (N=17) Mean (SD)	Atypical (N=15) Mean (SD)	P Value*
Age at Study entry	20.6(3.4)	23.5(4.2)	.01
Race (n=Caucasian)	7	12	.03
Duration of Illness (months)	8.6(8.1)	13.8(12.7)	.02
Age of Illness Onset	19.9(3.5)	22.7(4.4)	.17
PANSS Total	87.9(23.8)	70.9(14.3)	.08
PANSS Positive Sub-scale	21.1(5.8)	18.9(4.4)	.52
PANSS Negative Sub-scale	22.9(7.4)	17.1(5.3)	.25
CGI	4.5(1.0)	3.9(0.5)	.23

* by Fisher's exact test for continuous variables, and Kruskal-Wallis rank test for other continuous variables