ORIGINAL ARTICLE

Hippocampal Volume in First-Episode Psychoses and Chronic Schizophrenia

A High-Resolution Magnetic Resonance Imaging Study

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Background: It has been proposed that the hippocampus is a potential site for a neurodevelopmental lesion in schizophrenia. While smaller hippocampal volumes have been described in chronic schizophrenia, there have been few magnetic resonance imaging studies in first-episode psychosis. Furthermore, no studies have examined the specificity of this finding to first-episode schizophrenia, compared with first-episode affective psychosis.

Methods: Hippocampal and whole-brain volumes were estimated using high-resolution magnetic resonance imaging in 140 controls, 46 patients with chronic schizophrenia, and 32 patients with first-episode psychosis.

Results: Patients with chronic schizophrenia and first-episode psychosis had significantly smaller hippocampal volumes as compared with controls. Within the first-episode group, both patients with schizophrenia/schizophreniform psychosis and those with affective psychosis had smaller left hippocampal volumes as compared with controls. Smaller right hippocampal volumes were associated with age and illness duration in patients with chronic schizophrenia. Hippocampal volumes were not correlated with age of illness onset or medication dosage in either patient group.

Conclusions: These data show that smaller hippocampal volumes are present from the onset of illness. While these findings would support the neurodevelopmental model of schizophrenia, the finding of smaller left hippocampal volume in patients with first-episode schizophrenia and affective psychosis does not support the prediction that smaller hippocampi are specific to schizophrenia. The association of smaller right hippocampal volumes with increased illness duration in chronic schizophrenia suggests either that there is further neurodegeneration after illness onset or that bilateral small hippocampi predict chronicity.

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THE NEURODEVELOPMENTAL model of schizophrenia[1-3] proposes that structural brain changes in early life predispose an individual to the development of schizophrenia. Proponents of this model draw on several sources of evidence for support, including the higher incidence of obstetric complications, winter births, minor physical abnormalities, and soft neurologic signs in patients with schizophrenia. According to this model, structural brain changes are present prior to the onset of schizophrenia, specific to schizophrenia, and nonprogressive.

Neuropathological hippocampal abnormalities in schizophrenia[4,5] and the connections of the hippocampus to other brain regions, particularly the prefrontal cortex,[6-8] have implicated the hippocampus as a site for a neurodevelopmental lesion.[9,10] The nature of such a lesion is unclear, but Weinberger[11] has suggested that the lesion involves a subtle reduction of tissue mass. Smaller hippocampi have been found in 4[12-15] of 5[16] high-resolution magnetic resonance imaging (MRI) studies using slices of 1.5 mm or less, but in only 11[17-27] of 24[28-40] studies using slices thicker than 1.5 mm. Thinner slices allow delineation of hippocampal boundaries using anatomical landmarks,[41] rather than external landmarks[15,37] or semiautomated procedures.[31] The inconsistency of results across studies may be explained by the finding that hippocampal volumes can vary by 8% to 15% when estimated from slices greater than 3 mm.[41]

Most MRI hippocampal studies have examined patients with chronic illness,

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SUBJECTS AND METHODS

SUBJECTS

Consecutive first-episode inpatients were recruited from the Early Psychosis Prevention and Intervention Centre, Melbourne, Australia.[43] Study inclusion criteria were (1) age at onset between 16 and 30 years; and (2) currently psychotic as reflected by the presence of at least 1 symptom (either delusions, hallucinations, disorder of thinking and/or speech other than simple acceleration or retardation, and disorganized, bizarre, or markedly inappropriate behavior). *DSM-III-R* diagnoses[44] were based on medical record review and the Royal Park Multidiagnostic Instrument for Psychosis,[45] which was administered within 2 weeks of admission. There was no difference in the age ($t_{169} = 0.50$, $P = .62$) or sex ($\chi^2_1 = 0.31$, $P = .58$) of the study group compared with all first-episode Early Psychosis Prevention and Intervention Centre inpatients for the period 1995 to 1996. Patients with chronic schizophrenia were recruited from the Rehabilitation Unit, Royal Park Hospital, Melbourne. Diagnoses were based on clinical symptoms and medical record review using *DSM-III-R* criteria.[44] All patients with chronic schizophrenia had at least 2 years of neuroleptic exposure at the time of scanning. Healthy volunteers were recruited by approaching ancillary hospital staff and through advertisements. These subjects were recruited from similar sociodemographic areas as the patients.

All subjects were screened for comorbid medical and psychiatric conditions by clinical assessment and physical and neurologic examination. Exclusion criteria were a history of significant head injury, seizures, neurologic diseases, impaired thyroid function, steroid use, or *DSM-III-R*[44] criteria of alcohol or substance abuse or dependence. Control subjects with a personal or family history of psychiatric illness were excluded.

Two hundred twenty-nine subjects were recruited for the study but only 218 were included in the analysis (**Table 1**). Following scanning, 11 subjects were excluded; 6 patients with chronic schizophrenia (temporal lobe lesion, 2 patients; basal ganglia infarction, 1 patient; frontal lobe contusion, 1 patient; diagnosis revised to schizoaffective disorder, 2 patients); 4 first-episode patients (patient subsequently deemed not first-episode, 3 patients; steroid use prior to scanning, 1 patient); and 1 control subject (occipital lobe cyst).

Clinical information, including handedness,[46] premorbid IQ as assessed by the New Adult Reading Test,[47] and medication data (expressed in the relevant milligram equivalents[48]), was obtained from patient interview and medical record review (Table 1). The National Adult Reading Test has been shown to be stable over time in patients with schizophrenia[49] and provides a better estimate of the highest premorbid level of functioning than the Wechsler Adult Intelligence Scale–Revised,[50] which may yield reduced scores in patients with schizophrenia following the onset of illness.[51] First-episode patients were neuroleptic-naive prior to admission but had received antipsychotic medication for a mean of 30.8 days (SD = 32.4 days; range, 1-149 days) prior to scanning. Medication doses for patients with chronic schizophrenia were calculated for the 30 days prior to scanning. Thirteen patients with chronic schizophrenia had incomplete medication data. Written informed consent was obtained from all subjects. The study was approved by local research and ethics committees.

MRI PROTOCOL AND DATA ANALYSIS

All patients and 46 controls underwent scanning with a 1.5-Tesla scanner (Signa Horizon; General Electric Medical Systems, Milwaukee, Wis) at the Royal Melbourne Hospital. The remaining 97 control subjects were scanned at an identical scanner at Cabrini Hospital, Melbourne. Head movement was minimized by foam padding and straps across the forehead and chin. Patients received their normal medication on the day of scanning.

A 3-dimensional volumetric spoiled gradient recalled echo in the steady state sequence generated 124 contiguous, 1.5-mm coronal slices. Imaging parameters in the Cabrini and Royal Melbourne Hospitals were time-to-echo, 9 and 3.3 milliseconds; time-to-repetition, 36 and 14.3 milliseconds; flip angle, 35° and 30°; matrix size, 256 × 192 and 256 × 256; field of view, 20 × 15 cm and 24 × 24 cm matrix; voxel dimensions, 0.781 × 0.781 × 1.5 mm and 0.937 × 0.937 × 1.5 mm, respectively. Each scanner was calibrated fortnightly using the same proprietary phantom to ensure stability and accuracy of measurements. There were no significant differences in structural measures between scanners for control subjects (for whole-brain volumes, $t_{138} = 0.82$, $P = .41$; for total hippocampal volume, $t_{135} = 0.55$, $P = .58$). All subjects in analyses 2 and 3 below underwent scanning at the Royal Melbourne Hospital.

with few examining first-episode patients.[20,34,37,42] The available first-episode studies are limited by the control subjects used,[20,34,37,42] failure to account for the effect of whole-brain volume,[20,42] or the use of thick MRI slices.[20,34,37] To our knowledge, no MRI study using slices 1.5 mm or less has reported hippocampal volumes in a first-episode group. Furthermore, no study has addressed the specificity of structural hippocampal change in first-episode psychosis. We have addressed the methodological limitations of previous studies[10] by using thin MRI slices and reliable anatomical criteria for hippocampal delineation in a first-episode psychosis group, including patients with schizophrenia/schizophreniform and affective psychoses, compared with patients with chronic schizophrenia and controls.

RESULTS

Comparison of the 3 groups in analysis 1 revealed that there were no differences in height or handedness, although there were more female control subjects (χ^2_2=14.6, $P<.001$) and the first-episode subjects were younger (t_{215}=2.43, P=.02). In analysis 2 there were no sex, height, or handedness differences between the groups. Patients with chronic schizophrenia were older than first-episode patients (t_{105}=7.49, $P<.001$) and controls (t_{105}=7.82, $P<.001$). The control subjects had higher premorbid IQs than both chronic ($t_{105} = 2.25$, $P<.05$) and first-episode patients ($t_{105} = 3.81$, $P<.001$). The first-episode subgroups and controls (analysis 3) did not differ in sex, age, handedness, or height, although first-

Magnetic resonance imaging data were transferred from digital tape to an IBM 6000 RISC workstation (IBM North America, New York, NY) and analysed using ANALYZE 7.2 software (Mayo Clinic, Rochester, Minn). A code was used to ensure patient confidentiality and blind rating of data. A neuroradiologist reviewed all MRI films.

Hippocampal volumes were estimated using a manual tracing technique and defined anatomical criteria.[52] Hippocampal boundaries were defined as *posterior* (slice with greatest length of continuous fornix); *medial* (open end of the hippocampal fissure posteriorly, uncal fissure in the hippocampal body and medial aspect of ambient gyrus anteriorly); *lateral* (temporal horn of lateral ventricle); *inferior* (white matter inferior to the hippocampus); *superior* (superior border of hippocampus); and *anterior* (alveus was used to differentiate hippocampal head from amygdala). The anterior border was the most difficult to identify consistently and was aided by moving between slices before and after the index slice. Hippocampal length was estimated as the number of slices per hippocampus. One rater (D.V.) performed all hippocampal tracings included in the analyses. The intraclass correlation for intrarater reliability (D.V.), determined by blindly retracing 20 randomly selected images, was 0.85 and for interrater reliability (D.V. and M.C.) was 0.72 in 10 subjects.

Whole-brain volumes were estimated, with investigators blind to diagnosis, using a 3-dimensional morphometric procedure that included the cerebellum, brainstem, and ventricles but not cisterns or sulcal cerebrospinal fluid. A thresholding technique maximally separated brain and skull to produce minimum and maximum pixel values. These values were applied to all slices in a series of erosions and dilatations, the number of which was determined by the rater. Images were divided among 3 raters (D.V., N.B., P.T.) for whom interrater reliability on 10 images was 0.98.

STATISTICAL ANALYSIS

Three analyses were carried out on whole-brain and hippocampal volumes. The first included 140 controls and all patients (**Table 2**). Differences in whole-brain volume were assessed by a 1-way analysis of variance (ANOVA) defined by a 3-level (control, chronic, and first-episode) between-subjects group factor. Differences in hippocampal volume were assessed by a repeated-measures ANOVA defined by the same between-subjects group factor and a 2-level (right and left hippocampal volumes) within-subjects laterality factor.

The second set of analyses used corresponding 1-way and 2-way analysis of covariance designs to control for the possible confounding effects of concomitant variables. For whole-brain volume, the covariates were age, sex, height, and premorbid IQ. For hippocampal volume, the same 4 covariates were used, plus whole-brain volume (**Table 3**).

Premorbid IQ scores were available on 42 controls, 34 chronic, and all 32 first-episode psychosis cases. The control subgroup did not differ from the remaining 98 control cases in whole-brain volume ($t_{138} = 1.67$, $P = .98$) or left ($t_{138} = -0.10$, $P = .92$) and right ($t_{138} = -0.32$, $P = .75$) hippocampal volumes.

The third set of analyses examined the diagnostic specificity of structural differences by subdividing the first-episode patients into a subgroup of 16 with schizophrenia/schizophreniform disorder, and a subgroup of 10 with affective psychosis (8 with bipolar disorder and 2 with major depression). These 2 subgroups were compared with the 42 control cases from the second set of analyses (Table 3). The number of remaining first-episode patients (4 with schizoaffective disorder and 2 with psychotic disorder not otherwise specified) was too small to form a third subgroup and thus these patients were excluded.

Given the reduced size of the first-episode subgroups, it was decided to maximize power by including covariates found to be statistically significant from the second set of analyses. These covariates were sex ($t_{101} = -2.83$, $P = .006$) and premorbid IQ ($t_{101} = 2.75$, $P = .007$) for whole-brain volume, and whole-brain volume ($t_{100} = 6.41$, $P < .001$) only for hippocampal volume.

All pairwise mean comparisons (Table 3) employed a generalization of the Fisher least significant difference procedure,[53] which avoided the necessity of Bonferroni-correcting the assigned .05 α level. To compare the magnitude of mean differences, and to distinguish substantive from statistically significant results, the Cohen d standardized effect sizes[54] (plus 95% confidence intervals) were calculated from the pairwise comparisons. An effect size of 0.20 is typically regarded as being small, 0.50 as being moderate, and 0.80 as being large.[54] Associations among volume measures and demographic, clinical, and medication variables were assessed using Pearson product-moment correlations (**Table 4**).

episode schizophrenia/schizophreniform patients had lower premorbid IQs ($t_{65} = 3.90$, $P < .001$) (Table 1).

There were no significant differences between the chronic schizophrenia, first-episode psychotic, and control groups in whole-brain volume, either without the inclusion of covariates in analysis 1 ($F_{2,215} = 2.48$, $P = .09$) or when controlling for age, sex, height, and premorbid IQ in analysis 2 ($F_{2,101} = 1.36$, $P = .26$). There were no significant differences in whole-brain volume between the control group and first-episode subgroups ($F_{2,63} = 0.34$, $P = 0.7$) (Table 2).

Analysis 1 revealed significant differences in the hippocampal volumes of the chronic, first-episode, and control groups ($F_{2,215} = 21.16$, $P < .001$), but these differences did not vary between the left and right hippocampus ($F_{2,215} = 0.55$, $P = .58$). Subjects in all 3 groups had significantly larger right vs left hippocampal volumes ($F_{1,215} = 84.18$, $P < .001$) (Table 2). As an indication of the differences being observed, 93% of the patients with chronic schizophrenia and 81% of those with first-episode schizophrenia fell below the mean total hippocampal volume of the controls (**Figure 1**).

To ensure that these differences were not due to differences in hippocampal length (defined as the number of slices traced per hippocampus), subsidiary analyses were carried out on hippocampal length, covarying for whole-brain volume. There were no significant differences in mean right hippocampal length (controls, 22.9 ± 2.0; chronic schizophrenia, 23.2 ± 2.1; first-episode psychosis, 22.3 ± 2.0 [$F_{2,205} = 2.15$, $P = .12$]), nor in mean left

Table 1. Demographics of Subject Groups*

	Analysis 1			Analysis 2		
	Controls	Chronic Schizophrenia	First-Episode Schizophrenia	Controls	Chronic Schizophrenia	First-Episode Schizophrenia
No. of subjects	140	46	32	42	34	32
M/F	82/58†	40/6	25/7	30/12	31/3	25/7
Age, y	30 (12.5)	34.4 (8.4)	21.2 (3.1)‡	22.8 (6.1)	34.2 (9.4)†	21.2 (3.1)
Height, cm	174 (9.1)	174 (7.6)	174 (8.5)	177 (9.5)	175 (7.7)	174 (8.5)
Right-handed, %	91	90	83	91	85	83
Premorbid IQ§	. . .	. . .	. . .	111 (8.9)	105 (13.1)‡	101 (12.4)†
Age at first admission, y	. . .	20.6 (7.6)	21.2 (3.1)	. . .	19.9 (7.6)	21.2 (3.1)
Days receiving AP	. . .	31	30.8 (32.4) (n = 31)	. . .	31	30.8 (32.4) (n = 31)
Total AP dose, mg	. . .	21018 (16 153) (n = 33)	5384 (7983) (n = 31)	. . .	21786 (15 436) (n = 23)	5384 (7983) (n = 31)
Average daily AP dose, mg	. . .	656 (431) (n = 23)	164 (107) (n = 31)	. . .	668 (354) (n = 23)	164 (107) (n = 31)
Total lithium dose, mg	. . .	32000 (11 505) (n = 4)	36714 (45 121) (n = 7)	. . .	30167 (13 356) (n = 3)	36714 (45 121) (n = 7)
Total benztropine dose, mg	. . .	83.4 (40) (n = 7)	33.3 (42.3) (n = 18)	. . .	87.3 (42.7) (n = 6)	33.3 (42.3) (n = 18)
Total BDZ, mg	. . .	119 (256) (n = 18)	209 (323) (n = 23)	. . .	191 (324) (n = 9)	209 (323) (n = 23)
Total AD, mg	. . .	7256 (6045) (n = 9)	3537 (4707) (n = 4)	. . .	9058 (6574) (n = 6)	3537 (4707) (n = 4)

*Data are presented as mean (SD) unless otherwise indicated. AP indicates antipsychotics (expressed as milligram equivalents of chlorpromazine); BDZ, benzodiazepine (expressed as milligram equivalents of diazepam); AD, antidepressants (expressed as milligram equivalents of amitriptyline); and ellipses, not applicable. For the chronic schizophrenia group, all medication data were calculated for the 31 days prior to scanning (see text).

†$P<.001$.

‡$P<.05$.

§Available premorbid IQ data summarized in analyses 2 and 3.

hippocampal length (controls, 23.5 ± 2.1; chronic schizophrenia, 23.8 ± 2.4; first-episode psychosis, 22.8 ± 2.0 [$F_{2,205} = 2.15$, $P = .12$]).

The differences observed in analysis 1 were maintained when age, sex, height, premorbid IQ, and whole-brain volume were included as covariates (analysis 2, Table 3). There were significant group ($F_{2,100} = 5.40$, $P = .006$) and laterality ($F_{1,105} = 39.29$, $P<.001$) effects, but group differences did not vary according to left or right hippocampus ($F_{2,105} = 1.17$, $P = .31$). Planned comparisons indicated that the chronic and first-episode groups significantly differed from controls for both left and right hippocampal volumes. These significant differences corresponded to moderate effects on average, ranging from 0.406 to 0.586 in size, and represent adjusted hippocampal volumes that were smaller for patients with first-episode (right, 5.5% smaller; left, 8.1% smaller) and chronic schizophrenia (right, 8.1% smaller; left, 7.6% smaller). There were no significant differences between the 2 patient groups for either side.

There were significant differences in hippocampal volume among the 2 first-episode subgroups and controls ($F_{2,64} = 3.31$, $P = .04$) when controlling for whole-brain volume (analysis 3, Table 3). Paired comparisons revealed that control subjects had significantly larger left hippocampal volume than first-episode patients with schizophrenia ($t_{64} = 2.48$, $P = .02$) and affective psychosis ($t_{64} = 2.01$, $P<.05$). The 2 first-episode groups did not significantly differ from each other ($t_{64} = 0.79$, $P = .94$). Compared with the control group, adjusted left hippocampal volumes were 8.1% smaller for the schizophrenia/schizophreniform subgroup and 7.7% smaller for the affective psychosis subgroup (**Figure 2**).

No significant associations were found in either patient group between whole-brain volume measures and age, duration of illness, age at first admission, or medication dosage. A smaller right hippocampus was associated with longer illness duration in patients with chronic schizophrenia. There were no associations between hippocampal volumes and age at first admission or medication dosage. Hippocampal volumes, right and left, were associated with whole-brain volume in the control and first-episode groups, but only left hippocampal volume was associated with whole-brain volume in the patients with chronic schizophrenia. These associations between whole-brain/hippocampal measures and age/illness duration suggest that patients with chronic schizophrenia and longer illness duration have smaller right hippocampal but not smaller brain size (Table 4).

COMMENT

This study has identified smaller hippocampal volumes bilaterally in patients with chronic schizophrenia and first-episode psychosis, in comparison with controls. Analysis of patients with schizophrenia/schizophreniform psychosis and affective psychosis showed significantly smaller left hippocampal volumes than in control subjects. Right hippocampal volume was associated with increasing illness duration in patients with chronic schizophrenia.

	Analysis 3		First-Episode Psychoses Not Included in Analysis 3	
Controls	Schizophrenia/ Schizophreniform	Affective Psychoses	Schizoaffective	Other
42	16	10	4	2
30/12	14/2	7/3	4/0	0/2
22.8 (6.1)	20.6 (3.1)	21.8 (2.3)	19.8 (2.9)	27.0 (2.8)
177 (9.5)	175 (7.7)	170 (9.2)	177 (7.2)	169 (12.7)
91	81	80	100	100
111 (8.9)	99 (14.0)†	102 (12.2)	95.7 (7.9)	103.8 (10.3)
. . .	20.6 (3.1)	21.8 (2.3)	19.8 (2.9)	27.0 (2.8)
. . .	32.2 (38.9) (n = 15)	28.9 (23.4) (n = 9)	43 (30.9) (n = 4)	7 (0) (n = 1)
. . .	5552 (8920) (n = 15)	5225 (5411) (n = 9)	12250 (12 892) (n = 4)	600 (0) (n = 1)
. . .	129 (86.5) (n = 15)	214 (129) (n = 9)	233 (115) (n = 4)	85.7 (0) (n = 1)
. . .	7000 (0) (n = 1)	22550 (7446) (n = 5)	137250 (0) (n = 1)	. . .
. . .	29.8 (31.5) (n = 8)	15.4 (17.6) (n = 5)	74.5 (82.5) (n = 3)	. . .
. . .	393 (462) (n = 8)	130 (137) (n = 10)	293 (439) (n = 4)	. . .
. . .	10500 (0) (n = 1)	775 (813) (n = 2)	. . .	. . .

These differences in hippocampal volumes were not accounted for by differences in whole-brain volume, age, sex, height, premorbid IQ, or handedness. Whole-brain volumes did not differ for any of the patient groups as compared with controls.

The percentage difference in whole-brain volume found in our patients with chronic schizophrenia, though not significant, compares with previous neuropathological[55] and MRI findings.[56,57] A recent longitudinal MRI first-episode study[57] identified smaller whole-brain volumes at the illness onset and frontal lobe reduction in patients over the period of the study. DeLisi et al[34] found no differences in brain volume at illness onset but a reduction in hemispheric volume in patients 4 years after illness onset,[35,36] suggesting progressive structural changes. The current study found that age-related reduction in whole-brain volumes of our controls was not seen in the 2 patient groups, though the failure to detect such a reduction may be due to the narrower age range in the patient groups. No longitudinal MRI studies beyond the first 5 years of illness have been reported, although one computed tomographic study has reported progressive, ventricular change over a 3-year period in patients with schizophrenia.[58]

To our knowledge, our study is the first to demonstrate that smaller hippocampi are apparent from the outset of psychotic illness to a similar degree as observed in chronic illness. Previous studies that have assessed hippocampal volume in first-episode patients have suffered from several methodological problems. A study that identified smaller hippocampi in men with first-episode schizophrenia[20] did not account for whole-brain volumes and did not match patients with controls, 7 of whom had neurologic disorders. DeLisi et al[34] and Hoff et al[37] found no difference between patients with first-episode and chronic schizophrenia as compared with controls, but in those studies thick MRI slices and controls with neurologic disorders were used. Two first-episode studies that reported a higher percentage of abnormal ratings for medial temporal structures in patients with first-episode and chronic schizophrenia as compared with controls were limited by the use of qualitative ratings.[59,60]

Fukuzako et al,[13,42] using thin MRI slices, ascribed smaller hippocampal volumes in chronic and first-episode patients to shortening of the hippocampus, but failed to report volumes in the first-episode group.[42] Further, while patients with chronic schizophrenia were well-matched to controls,[13] there was no matching for the first-episode patients.[42] Also, height and whole-brain volume were not controlled for in the first-episode study and, to adjust for the sex ratio difference between the groups, they adjusted the female hippocampal length to that of the males.[42] In contrast to these findings, our results in chronic schizophrenia and first-episode psychosis suggest that smaller hippocampi could not be accounted for by reduced length.

Smaller hippocampal volumes were not specific to the first-episode patients with schizophrenia/schizophreniform psychosis but were also seen in first-episode affective psychosis. Previous reports in bipolar disorder have described ventricular enlargement,[61,62] smaller right hippocampi in men,[40] and no hippocampal area change.[63] The present findings, suggesting nonspecific hippocampal volume reduction, must be regarded as preliminary owing to the small numbers in each subgroup and possible diagnostic instability in first-episode patients assessed at an early stage.[64] However, diagnostic stability in our sample, using a comprehensive assessment method,[45] is approximately 90% at 2 years (unpublished data, 1997), which is higher than other first-episode samples.[64] Further, the failure to identify smaller right hippocampal volumes in the first-episode subgroups may also be owing to the small numbers in each subgroup.

Neuropathological studies in schizophrenia, some of which have detected smaller hippocampi,[65-67] support the concept of an early, nonprogressive lesion of the hippocampus.[2,4,5] The evidence supporting a neurodegenerative model of schizophrenia is scant,[68] although there have been recent findings from longitudinal MRI studies of reductions in the volumes of the frontal[57] and temporal lobes, but not the hippocampi,[36] in first-episode patients. Our finding of an association between smaller right hippocampal volume and increasing illness duration in chronic schizophrenia would support the concept of biological toxicity of illness,[69] in which repeated episodes or continuous unremitting symptoms lead to hippocampal shrinkage. This explanation would, however, also predict progressive left hippocampal volume reduction. An alternative explanation is that patients with smaller hippocampi bilaterally are more likely to have a chronic course. Prospective longitudinal

Table 2. Absolute Whole-Brain and Hippocampal Volumes*

	No. of Patients	Whole-Brain Volume, mm³	Percent Difference†	Right Hippocampus, mm³	Percent Difference	Left Hippocampus, mm³	Percent Difference
Analysis 1							
Chronic schizophrenia	46	1 326 634 (122 258)	3.3	2897 (319)	10.1	2705 (317)	11.4
First-episode psychosis	32	1 328 485 (157 792)	3.2	2931 (408)	9.0	2709 (448)	11.2
First-episode schizophrenia	16	1 341 754 (134 896)	2.2	2939 (392)	8.8	2711 (521)	11.2
First-episode affective	10	1 376 679 (166 654)	–0.3	3051 (502)	5.3	2775 (425)	9.1
First-episode schizoaffective	4	1 232 490 (195 961)	10.2	2709 (217)	15.9	2612 (264)	14.4
First-episode other	2	1 132 898 (36 951)	17.4	2713 (7)	15.8	2560 (454)	16.1
Controls	140	1 372 088 (144 437)	. . .	3222 (401)	. . .	3052 (373)	. . .
Analyses 2 and 3							
Chronic schizophrenia	34	1 345 159 (126 991)	4.4	2885 (337)	10.2	2763 (333)	9.8
First-episode psychosis	32	1 328 485 (157 792)	5.6	2931 (408)	8.8	2709 (448)	11.5
First-episode schizophrenia	16	1 341 754 (134 896)	4.6	2939 (392)	8.5	2711 (521)	11.5
First-episode affective	10	1 376 679 (166 654)	2.1	3051 (502)	5.0	2775 (425)	9.4
First-episode schizoaffective	. . .	. . .	. . .	. . .	. . .	. . .	. . .
First-episode other	. . .	. . .	. . .	. . .	. . .	. . .	. . .
Controls	42	1 406 662 (133 087)	. . .	3213 (380)	. . .	3062 (355)	. . .

*Data are presented as mean (SD) unless otherwise specified.
†Percent smaller compared with normal controls.

Table 3. Adjusted Whole-Brain and Hippocampal Volume Means (Analyses 2 and 3)*

	No. of Patients	Adjusted Volumes, mm³†	Percent Difference‡	Compared With Chronic Schizophrenia§			Compared With First-Episode Psychosis¶		
				t	*P*	Effect Size‖	*t*	*P*	Effect Size
Analysis 2: Chronic/First-Episode/Controls									
Whole-brain									
Chronic	34	1 355 246 (± 51 271)	2.5	. . .	. . .	. . .	. . .	. . .	. . .
First-episode	32	1 340 075 (± 46 371)	3.6	–0.402	.69	–0.080 (± 0.395)	. . .	. . .	. . .
Controls	42	1 389 670 (± 41 123)	. . .	0.943	.35	0.188 (± 0.395)	1.608	.11	0.320 (± 0.395)
Right hippocampus									
Chronic	34	2903 (± 139)	8.0	. . .	. . .	. . .	. . .	. . .	. . .
First-episode	32	2986 (± 126)	5.4	0.814	.42	0.163 (± 0.397)	. . .	. . .	. . .
Controls	42	3157 (± 112)	. . .	2.569	.01	0.514 (± 0.397)	2.031	.04	0.406 (± 0.397)
Left hippocampus									
Chronic	34	2779 (± 135)	7.6	. . .	. . .	. . .	. . .	. . .	. . .
First-episode	32	2765 (± 123)	8.0	–0.138	.89	–0.028 (± 0.397)	. . .	. . .	. . .
Controls	42	3006 (± 109)	. . .	2.356	.02	0.471 (± 0.397)	2.931	.004	0.586 (± 0.397)
Analysis 3: First-Episode Subgroups/Controls				Compared With First-Episode Schizophrenia			Compared With First-Episode Affective Psychosis		
Whole-brain									
First-episode schizophrenia	16	1 363 983 (± 65 042)	2.4	. . .	. . .	. . .	. . .	. . .	. . .
First-episode affective psychosis	10	1 390 064 (± 73 700)	0.5	0.535	.59	0.135 (± 0.504)	. . .	. . .	. . .
Controls	42	1 396 938 (± 37 802)	. . .	0.826	.41	0.208 (± 0.504)	0.165	.87	0.042 (± 0.504)
Right hippocampus									
First-episode schizophrenia	16	3009 (± 167)	5.4	. . .	. . .	. . .	. . .	. . .	. . .
First-episode affective psychosis	10	3070 (± 209)	3.5	0.459	.65	0.115 (± 0.499)	. . .	. . .	. . .
Controls	42	3182 (± 103)	. . .	1.750	.08	0.438 (± 0.499)	0.956	.34	0.239 (± 0.499)
Left hippocampus									
First-episode schizophrenia	16	2785 (± 166)	8.1	. . .	. . .	. . .	. . .	. . .	. . .
First-episode affective psychosis	10	2795 (± 208)	7.7	0.079	.94	0.020 (± 0.499)	. . .	. . .	. . .
Controls	42	3029 (± 102)	. . .	2.481	.02	0.620 (± 0.499)	2.009	<.05	0.502 (± 0.499)

*Data are presented as mean (95% confidence interval width) unless otherwise specified.
†Whole-brain volume means adjusted for age, sex, height, and National Adult Reading Test score. Hippocampal volume means adjusted for age, sex, height, New Adult Reading Test score, and whole-brain volume.
‡Percent smaller compared with normal controls.
§For analysis 3, compared with first-episode schizophrenia.
‖Negative values indicate effect in direction of column comparison group.
¶For analysis 3, compared with first-episode affective psychosis.

Table 4. Correlation Coefficients Between Hippocampal Volumes, Whole-Brain Volume, and Clinical Characteristics

	Whole-Brain			Right Hippocampus			Left Hippocampus		
	Controls	First-Episode	Chronic	Controls	First-Episode	Chronic	Controls	First-Episode	Chronic
Whole-brain volume	. . .	. . .	. . .	0.56*	0.63*	0.29	0.51*	0.63*	0.50*
Age, y	−0.28*	−0.11	−0.12	−0.14	0.02	−0.26	−0.12	−0.01	−0.27
Height, cm	0.49†	0.34	0.43*	0.33†	0.21	0.17	0.27*	0.42‡	0.20
Premorbid IQ	0.34‡	0.50*	0.18	0.05	0.19	0.20	0.02	0.32	0.01
Illness duration, y	. . .	−0.10	−0.15	. . .	−0.21	−0.30‡	. . .	−0.04	−0.16
Age at onset, y	. . .	−0.07	−0.08	. . .	−0.08	0.06	. . .	−0.04	−0.11
Antipsychotic dose, mg	. . .	−0.15	0.08	. . .	−0.17	0.02	. . .	0.04	0.09

*P<.005.
†P<.001.
‡P<.05.

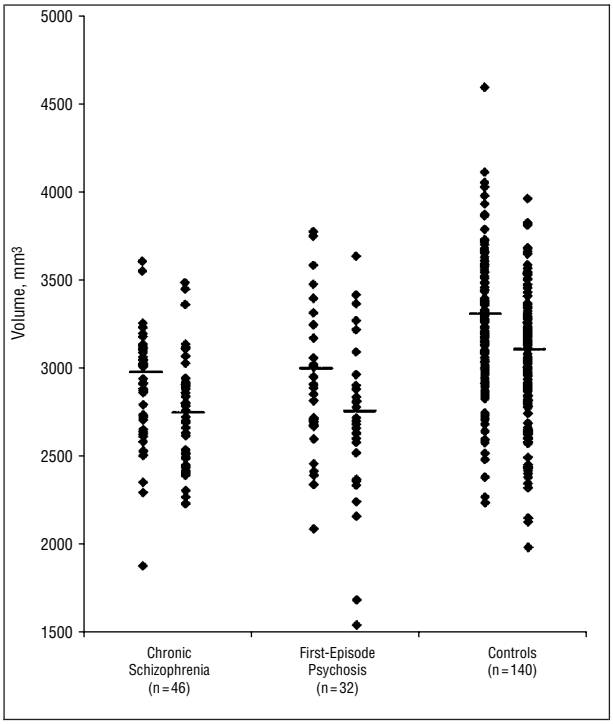

Figure 1. *Right (first column) and left (second column) unadjusted hippocampal volumes for each subject group. Bar indicates mean value.*

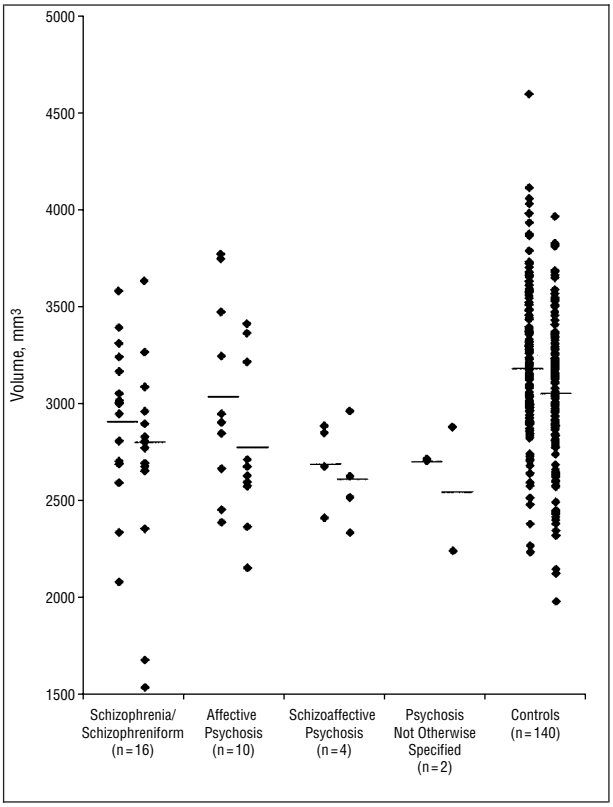

Figure 2. *Right (first column) and left (second column) unadjusted hippocampal volumes for first-episode subgroups and controls. Bar indicates mean value.*

studies, ideally beginning with prepsychotic individuals,[70] are required to address these possibilities.

While our findings are partially consistent with a neurodevelopmental model, alternative explanations, such as medication and chronic stress, may be relevant. A medication effect is unlikely for 2 reasons. First, medication dosage was not associated with hippocampal volume in any patient group. Second, antipsychotic-mediated hippocampal volume reduction in the first-episode group would need to have occurred, to the same degree as in patients with chronic schizophrenia, within 31 days of treatment. The "cortisol-cascade hypothesis"[71] may be relevant to hippocampal shrinkage given findings from both animal[71,72] and human literature[71,73,74] that chronic stress–induced cortisol secretion may lead to hippocampal degeneration. The finding of smaller left, rather than bilateral, hippocampal volumes would, however, be difficult to explain as an effect of either stress or medication.

There are several methodological limitations of this study. First, diagnosis in a first-episode group may alter following first presentation,[64] emphasizing the importance of a longitudinal approach. Second, the finding of smaller left hippocampi in the first-episode subgroups, but a bilateral difference in the combined first-episode group, may be due to the small numbers in the subgroups. This finding needs to be replicated with larger sample sizes. Third, the finding of an association between illness duration and right hippocampal volume in the chronic schizophrenia group, but not the first-episode group, may be due to a lack of variance in illness duration in the first-episode patients. Fourth, there was no correction for variations of head position during scanning, although this is unlikely to be problematic with

our thin-slice technology. Unless the positioning affects subject groups differentially, any effect from this will only act to reduce the effect size being observed; that is, would make the results more conservative. Reformatting MRI data into an oblique plane perpendicular to the long axis of the hippocampus has been suggested as a means of correcting for variations in head position.[75] The reformatting of rectangular voxels, however, may lead to blurring of anatomical boundaries,[76] resulting in a loss of anatomical resolution.

Our finding of bilaterally smaller hippocampal volume in chronic schizophrenia is consistent with a recent meta-analysis of MRI hippocampal studies in schizophrenia.[75] Further, our results in first-episode patients identified bilaterally smaller hippocampi soon after illness onset, which addresses one of the recommendations for further study made by Nelson et al.[75] While our findings provide support for the neurodevelopmental hypothesis by suggesting that hippocampal abnormalities are present at illness onset, they support neither the prediction that such changes are specific to schizophrenia nor the prediction that the lesion is nonprogressive. The further investigation of these latter 2 predictions requires longitudinal studies beginning with a large cohort of high-risk individuals prior to the onset of psychosis.

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