Duration of illness and treatment effects on hippocampal volume in male patients with schizophrenia

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Background Reduced hippocampal volume is a consistently described structural abnormality in schizophrenia but its cause and timing are not known.

Aims To examine the relationship of duration of schizophrenic illness and treatment effects with hippocampal volumes.

Method Quantitative 1.5 T magnetic resonance imaging brain scans of young male patients in the early stage of schizophrenic illness were compared with those of chronically ill older patients. Scans were also acquired for controls matched to both patient groups for age and handedness. Duration of illness was recorded and severity of symptoms assessed with the Positive and Negative Syndrome Scale.

Results The patients with schizophrenia had smaller hippocampal volumes than the controls. The volume reduction was larger in older patients than in young, compared with age-matched controls. In the early illness group atypical antipsychotics rather than haloperidol were associated with larger hippocampal volumes even after controlling for differences in illness severity.

Conclusions The greater reduction of hippocampal volume in people with chronic *v.* early illness, after controlling for illness severity and age, supports the hypothesis of progressive hippocampal reduction in males with schizophrenia. Atypical antipsychotics early in illness may protect against this.

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Reviews of structural magnetic resonance imaging (MRI) studies in schizophrenia consistently find reduction in hippocampal volume in patients compared with controls (Wright *et al*, 2000). The decrease is usually less than 10% (0.5 ml) of the total absolute hippocampal volume in a given sample. These reductions in volume may be a consequence of neurodevelopmental events preceding the onset of illness, and/or may occur after illness onset. In a cross-sectional study, Velakoulis *et al* (1999) reported left hippocampal volume reductions in both treatment-naïve patients with first-episode psychosis and patients with chronic schizophrenia, but right hippocampal volume reduction only in the latter. This suggests that hippocampal volumes continue to decrease after illness onset. That study was limited by its failure to use both young and old control groups who were matched to first-episode and chronic illness groups for age and gender.

METHOD

Our study was cross-sectional in design and assessed potential differences in the volume of the hippocampus between patients in the first few years of their illness and patients who were chronically ill. The study design is unique in that we matched participants with early illness to a young control group and those with chronic illness to an older control group. We also eliminated the confounding effects of gender and handedness by studying only right-handed men. Candidates for both patient and control groups were excluded if they reported any clinically significant neurological or medical disorder, a history of head trauma with loss of consciousness, current substance misuse, a lifetime history of substance dependence or use of ecstasy or phencyclidine (PCP) on more than two occasions.

Our *a priori* hypotheses were that the patients would have smaller hippocampal volumes than the control groups 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 hippocampal volume after controlling for age, severity of illness and intracranial cavity volume 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.

Participants

Ninety-three right-handed male patients who met DSM–IV criteria for schizophrenia or schizophreniform disorder (American Psychiatric Association, 1994) were recruited from University of North Carolina Hospitals and Duke University Medical Center from August 1997 to July 1999. Patients 16–30 years old with less than 5 years' total duration of illness were assigned to an early phase of illness study group (n=34), while patients 31–60 years old with more than 10 years' duration of illness constituted the chronic illness group (n=22). A total of 93 patients were screened and 56 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 artefacts on their scans. Several people in the early illness group were also participating in a randomised clinical trial comparing haloperidol with olanzapine (Lieberman *et al*, 2003). Participants in our study underwent a medical screening, the Edinburgh Handedness Inventory (Oldfield, 1971) to select right-handed individuals and the Structured Clinical Interview for DSM–IV Axis I Disorders (SCID; First *et al*, 1995).

For the control groups, 14 right-handed men who had a similar age range to patients in the early illness group and 12 right-handed men who had a similar age range to the patients in the chronic illness group were also recruited. Exclusion criteria were any Axis I DSM–IV psychiatric disorder and a lifetime history of substance misuse or dependence determined using a SCID interview. Patients' symptoms were evaluated with the Positive and Negative Syndrome Scale (Kay *et al*, 1987). The duration of illness was recorded, with the onset considered to be the point at which the patient first met the diagnostic criteria

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for schizophrenia. This was determined by thorough chart review, patient and family interview and discussion with the patient's treating physician.

Imaging protocol and data analysis

Participants were scanned with a GE Signa Advantage system (GE Healthcare Technologies, Waukesha, Wisconsin, USA) operating at 1.5 T. The series used for this study was acquired as a three-dimensional (3D) inversion recovery prepped axial spoiled gradient; fast spoiled gradient recalled axial plane, 3D acquisition time to echo (TE) 60 s; repetition time (TR) 15 ms, flip angle 20°, field of view 24 × 24 cm, bandwidth 16 kHz (125 Hz/pixel), matrix 256 × 256 × 124 slices, slice thickness 1.5 mm, number of excitations 1. 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 (Santa Clara, California, USA) using a three-dimensional software package (IRIS, University of North Carolina, Chapel Hill, NC, USA). Hippocampal segmentations included the hippocampus proper, the subiculum, the fimbria and subsplenial gyrus (Fig. 1). We used the sagittal plane to separate the hippocampus from the amygdala, with the alveus and/or the uncal recess of the temporal horn to separate the structures. More medially in the sagittal plane, the axial view was used at the level of the tuber cinerium, mamillary bodies and optic tracts. This corresponds to the level of the hippocampal–amygdala transition area in the axial plane. This area 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 (Convit *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.

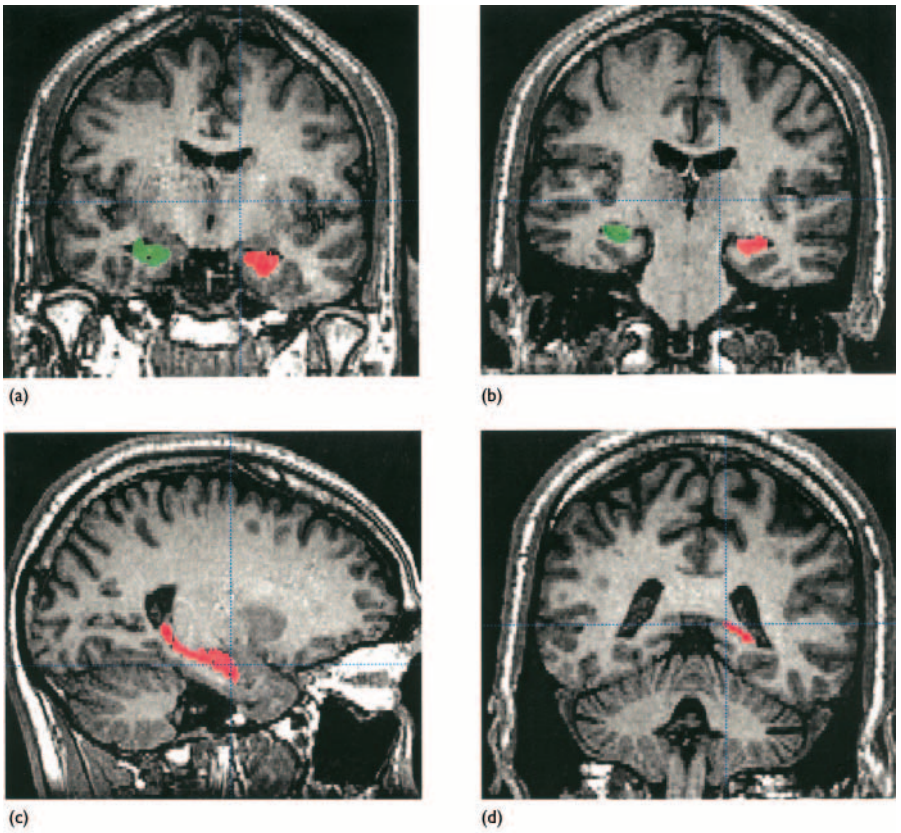

Fig. 1 Hippocampus on IRIS three-dimensional software. Red areas show right hippocampus; green areas show left hippocampus.

The superior hippocampal border was the alveus. The inferior border continued to be the parahippocampal region, and the lateral border was the temporal horn of the lateral ventricle or temporal stem.

Segmentation of the intracranial cavity

Analysis of the intracranial cavity volume was performed on a Sun Microsystems workstation and processed using MRX software (GE, Schenectady, NY, USA) 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 T_2-weighted images) to segment tissue types. Details of this method of tissue segmentation have been described by Kikinis *et al* (1992). After segmentation, a mask corresponding to the intracranial cavity was developed from the segmented images, which allowed elimination of non-brain tissues from the images. After disconnecting the brain from the extra-axial structures, the brain tissue in each slice was highlighted, allowing computation of the total intracranial cavity volume, which was the sum of grey and white matter and both intracerebral and extracerebral cerebrospinal fluid volumes.

All measurements were completed by a single rater (S.A.S.). The reliability series consisted of 15 scans, 3 from each of five participants. The scans were then put in a random order before being evaluated by S.A.S., who was masked to diagnosis, and were measured within a 4-month period. Intra-rater reliability was 0.86 for the left hippocampus and 0.88 for the right hippocampus; for the intracranial cavity it was 0.99.

Statistical analysis

The analyses had two principal objectives: first to determine whether patients had smaller hippocampal volumes than controls and whether the control–patient difference increased with age, and second, to explore the effects of duration of illness on hippocampal volumes in both groups of patients after controlling for the effects of age and symptom severity.

To achieve the first objective, a mixed model was used to compare each patient group with its corresponding age-matched

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control group and determine whether the patient–control difference increased with age. The analysis controlled for intracranial cavity volume by including it as a covariate in the model. The left and right hippocampal volumes were treated as repeated measures in order to address the high degree of 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 intracranial cavity 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 patients in the chronic group 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 patient groups using mixed model analyses, in which the possibility of differential drug effects were examined using antipsychotic drug type (atypical *v.* typical) as a between-subject factor, hemisphere as the repeated measure, and age, duration of illness, PANSS total score and intracranial cavity volume as covariates.

Data were not transformed in the second and third set of analyses, since the residuals of the outcome variable, hippocampal volume, were normally distributed. Distribution of duration of illness was skewed, but this was a continuous variable included in the model as a covariate and did not need to be normally distributed. More importantly, we believe that the duration of illness in its original scale is clinically more meaningful. The data from patients with longer duration of illness in each group are as informative as data from patients with shorter durations in relation to the study question we are pursuing. Given the fair number of cases with longer duration, we are convinced that our findings are reliable, and not due to the influence of outliers.

RESULTS

Comparison of patient and control groups

There was no significant difference between the mean age of patient subgroups and their respective gender-matched comparison groups: early illness group mean age 21.9 years (s.d.=3.9), controls 22.7 years (s.d.=2.8); chronic illness group mean age 42.8 years (s.d.=8.6), and controls 41.1 years (s.d.=7.3). With respect to ethnicity, 62% of the early illness patient group, 50% of the chronic illness patient group, 86% of the early illness control group and 58% of the chronic illness control group were White, and the majority of the other group members were African American. There was no significant difference in ethnic composition between the four groups (P=0.18 by Fisher's exact test). The groups also had comparable socio-economic status, as measured by the amount of parental education (P=0.29 by Fisher's exact test). In each of the four groups, more than three-quarters of participants had at least one parent with a high-school or higher education.

Table 1 summarises the clinical characteristics of the early illness and chronic illness patient groups. Ten of the 34 patients with early illness had a diagnosis of schizophreniform disorder and 24 had a diagnosis of schizophrenia. As anticipated, patients with chronic illness were older, with longer duration of illness and more hospitalisation compared with 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 Clinical Global Impression (CGI; Guy, 1976) scores or age of onset. At the time of scanning, 17 patients in the early illness group were taking a typical antipsychotic medication (all haloperidol), 15 were taking an atypical antipsychotic medication (12 olanzapine, 3 risperidone), 1 was taking both typical and atypical antipsychotic medications (clozapine and molindone) and 1 was participating in a double clinical trial with antipsychotic medication unknown. In the chronic illness group, only 5 patients were taking typical medications (3 haloperidol, 1 trifluoperazine and 1 thiothixene) and 17 were taking atypical medications (6 olanzapine, 8 clozapine and 3 risperidone).

The absolute volumes of the left and right hippocampi in the four study groups are given in Table 2. In the first analysis of these findings, right hippocampal volumes were found to be greater than left hippocampal volumes for both patients and controls (mean difference 0.12 ml, s.d.=0.03, $F_{1,78}$=18.83, P=0.001). There was a significant association of intracranial cavity volume with hippocampal volume ($F_{1,75}$=21.37, P=0.001). The partial correlation of intracranial cavity to hippocampal volume after adjusting for age was r=0.52 ($P<0.001$). The major finding from this analysis was the significant reduction in hippocampal volumes in both patient groups relative to their respective control groups ($F_{1,75}$=9.1, P=0.0034). The group × side interaction was not significant.

Table 1 Clinical characteristics of participants with schizophrenia

	Early illness group (n=34)	Chronic illness group (n=22)
Age at study entry, years: mean (s.d.)	24.9 (8.8)	37.1 (11.8)
Duration of illness, months: mean (s.d.)	12.41 (11.8)	250.43 (101.06)
Age at illness onset, years: mean (s.d.)	21.14 (4.03)	21.78 (3.8)
PANSS		
Total score: mean (s.d.)	78.55 (21.17)	86.27 (22.83)
Positive sub-scale	19.97 (5.25)	22.1 (6.9)
Negative sub-scale	19.63 (6.96)	22.1 (6.9)
CGI score: mean (s.d.)	4.14 (0.92)	4.5 (1.15)
Medication when scanned, *n*		
Typical antipsychotic	15	7
Atypical antipsychotic	17	15
Both	1	0
Unknown	1	0

CGI, Clinical Global Impression; PANSS, Positive and Negative Syndrome Scale.

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Table 2 Hippocampal and intracranial cavity volumes

Region	Volume (ml)							
	Early illness group				Chronic illness group			
	Patients (n=34)		Controls (n=14)		Patients (n=22)		Controls (n=12)	
	Mean	(s.d.)	Mean	(s.d.)	Mean	(s.d.)	Mean	(s.d.)
Intracranial cavity	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)

Moreover, numerically, the reduction was greater in patients in the chronic illness group than in the early illness group, even though the difference was not statistically significant. The model-estimated reduction was 0.16 ml, s.d.=0.09 (t_{75}=1.76, P=0.08), or 5.5%, in the early illness group, compared with 0.26 ml, s.d.=0.10 (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 illness group (Cohen, 1988).

The results were the same when the analyses were repeated after removing the data for 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 volume

The strength of this study design was the inclusion of the healthy control groups matched with patient groups on major demographic characteristics. Therefore, separate mixed models were used to examine the effects of duration of illness on hippocampal volumes in patients in the early illness and chronic illness groups, controlling for age and intracranial cavity volume. 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 illness 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 chronic illness group (t_{42}=−0.46, P=0.65). The other analysis controlling for symptom severity (PANSS total score) in addition derived similar results for duration of illness, and the symptom severity effect was non-significant (P>0.50 for either group).

Effect of illness duration and type of antipsychotic in the early illness group

The numbers of patients in the early illness group taking typical and atypical antipsychotic drugs, as well as their demographic and clinical characteristics, are listed in Table 3. Patients taking atypical drugs were older, more of them were White and their symptoms were milder as measured by PANSS total, PANSS negative and CGI scores, but their age at onset and duration of illness were similar to those of the other patients in this group.

After controlling for age, intracranial cavity volume and symptom severity (PANSS total score), 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 for patients taking atypical antipsychotics 5.8 ml, s.d.=0.51; for patients taking typical antipsychotics the mean volume was 5.10 ml, s.d.=0.52; (Fig. 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) (Fig. 3). *Post hoc* tests indicated that patients with longer duration of illness who were treated with an atypical antipsychotic drug had larger hippocampal volumes (t_{26}=3.02, P<0.01; correlation of hippocampal volume and duration of illness for patients with early illness taking 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 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 antipsychotics adjusted for age and intracranial cavity volume: r=−0.21, n=17, P=0.45). The analyses were repeated controlling for the effects of ethnicity, positive symptoms and negative symptoms; as there was no effect of these factors on hippocampal volume, they were dropped in the final model.

Within the chronic illness 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 a matched comparison group, even after adjusting for the effects of age, hemisphere and intracranial volume. The finding of decreased

Table 3 Clinical characteristics of patients with early illness categorised by type of medication

	Typical antipsychotic (n=17)	Atypical antipsychotic (n=15)	P[1]
Age at study entry, years: mean (s.d.)	20.6 (3.4)	23.5 (4.2)	0.01
White, n	7	12	0.03
Duration of illness, months: mean (s.d.)	8.6 (8.1)	13.8 (12.7)	0.02
Age at illness onset, years: mean (s.d.)	19.9 (3.5)	22.7 (4.4)	0.17
PANSS			
Total	87.9 (23.8)	70.9 (14.3)	0.08
Positive sub-scale	21.1 (5.8)	18.9 (4.4)	0.52
Negative sub-scale	22.9 (7.4)	17.1 (5.3)	0.25
CGI score: mean (s.d.)	4.5 (1.0)	3.9 (0.5)	0.23

CGI, Clinical Global Impression; PANSS, Positive and Negative Syndrome Scale.
1. By Fisher's exact test for continuous variables, and Kruskal–Wallis rank test for other continuous variables.

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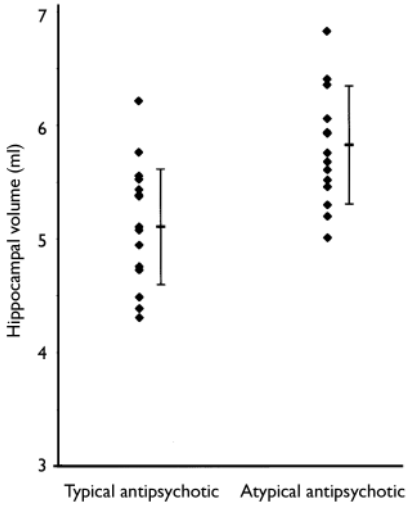

Fig. 2 Hippocampal volume by drug type in patients with early illness.

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 patients with chronic illness, which is consistent with the findings of Velakoulis *et al* (1999), as well as confirming a previous report by our group of greater volume reduction in patients with chronic illness compared with people with a first psychotic episode and controls (Bogerts *et al*, 1993). The greater reduction of hippocampal volumes in the chronic illness *v.* control group comparison than in the early illness *v.* control group comparison was confirmed using effect size analysis, which measures the magnitude of the effect independent of sample size.

One possible explanation for the smaller hippocampal volumes in patients with chronic illness compared with the early illness group is that there are progressive changes in the hippocampus in men with schizophrenia over the course of their illness. Alternatively, our chronic illness group might have recruited patients who were more severely ill than is typical of people with long-standing schizophrenic disorder. However, we compared the two patient groups with respect to commonly accepted measures of illness severity (PANSS total sub-scale scores, CGI scores and age at illness onset) and found no difference in illness severity between them. This led us to conclude that the finding of increased hippocampal volume reduction in the chronic illness group 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 10 years of the illness. There was an unanticipated association of larger hippocampal volume 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 the assignment of patients in the early illness group to treatment with haloperidol or atypical antipsychotic medication was randomised in the context of the clinical trials in which the patients were participating, there was no association with drug class and type of patient. This suggests that male 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. Neurogenesis of hippocampal cells can continue into adult life (Eriksson *et al*, 1998; Kempermann *et al*, 2000), so it is possible that people with schizophrenia lack or have diminished capacity to regenerate cells in adolescence and adulthood. In this context, atypical antipsychotic drugs might stimulate pathways involved in supporting cellular plasticity and resilience, as has been demonstrated with mood-stabilising and antidepressant drugs (Manji *et al*, 2000; Santarelli *et al*, 2003). Unlike antidepressants, which increase hippocampal neuronal survival and differentiation in response to stress in part by increasing levels of brain-derived neurotrophic factor (Malberg *et al*, 2000), both typical and atypical antipsychotics reduce levels of this factor in the rat hippocampus (Lipska *et al*, 2001). However, antipsychotics have been reported to increase another neurotrophic factor, Bcl-2 (an inhibitory protein of

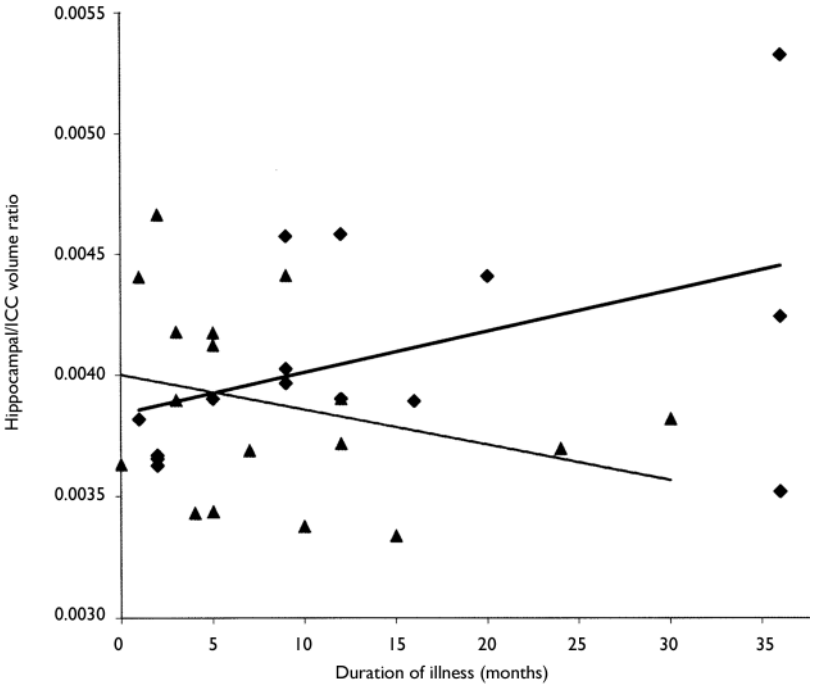

Fig. 3 Relationship between hippocampal volume and duration of illness taking atypical (◆) or typical (△) antipsychotic medication. ICC, intracranial cavity.

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apoptosis), in the temporal lobes of people with schizophrenia (Jarskog *et al*, 2000). Perhaps atypical antipsychotic medications exert a neuroprotective effect by upregulating Bcl-2 in the hippocampi of young male patients with schizophrenia.

Atypical antipsychotic medications also modulate glutamate-mediated activity in the hippocampus. Olney & Farber (1995) proposed that reduced *N*-methyl-D-aspartate (NMDA) receptor function in schizophrenia resulted in a disinhibition of glutamate in specific corticolimbic circuits, with consequent neurotoxic effects. Atypical antipsychotic drugs can antagonise 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

- Male patients with schizophrenia who have no history of substance dependence or current substance misuse have smaller hippocampal volumes than age- and gender-matched controls.
- Our findings suggest a progressive hippocampal volume reduction during the course of schizophrenic illness in male patients.
- Treatment with atypical antipsychotic medication early in the course of illness may protect against hippocampal reduction in these patients.

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 assignment to treatment with typical or atypical antipsychotic medications was not random in the group of patients with chronic illness.
- Our findings cannot be generalised to women patients or to those with a history of substance misuse.

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