# Hippocampal Volume Change in Schizophrenia

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***Objective:*** Patients with schizophrenia show reductions in hippocampal volume. However, the time course of these changes is still unresolved. The aim of this study is to examine the extent to which hippocampal volume change in patients with schizophrenia is confounded by effects of age and/or antipsychotic medication.

***Method:*** Between 1995 and 2003, two structural magnetic resonance imaging brain scans were acquired from 96 patients with *DSM-IV*–diagnosed schizophrenia and 113 healthy subjects within an interval of approximately 5 years. Hippocampal volume change was measured and related to age and cumulative medication intake during the scan interval.

***Results:*** Patients with schizophrenia and healthy controls demonstrated significantly different age-related trajectories of hippocampal volume change. Before the age of 26 years, patients with schizophrenia showed increased volume loss relative to controls. In contrast, after the age of 40 years, controls showed larger volume loss than patients with schizophrenia. Higher exposure to atypical antipsychotic medication was related to a smaller decrease in hippocampal volume over time.

***Conclusion:*** Our findings suggest progressive hippocampal volume loss in the early course of the illness in patients with schizophrenia but not in the more chronic stages of the illness. The relationship between larger exposure to atypical antipsychotic medication and smaller hippocampal volume loss during the interval may suggest neuroprotective effects of these agents on hippocampal volume.

*J Clin Psychiatry 2010;71(6):737–744*



***Submitted:*** *July 28, 2008; accepted January 30, 2009.*
***Online ahead of print:*** *January 12, 2010 (doi:10.4088/JCP.08m04574yel).*
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Patients with schizophrenia show reductions in hippocampal volume relative to healthy subjects (for meta-analyses, see references 1–3). This is of interest since decreased hippocampal volumes have been associated with decreased memory and poorer executive function[4] and aberrant cognitive function is one of the key features of schizophrenia.[5] Despite the volume differences reported in cross-sectional studies, longitudinal brain imaging studies[6–8] have failed to find hippocampal volume change over time in patients with schizophrenia as compared to healthy controls. However, these studies[6–8] examined first-episode patients and patients with chronic schizophrenia within a limited age range (20–35 years), making it difficult to disentangle the influence of age-related and illness-related changes on hippocampal volume. In addition, it is unclear to what extent hippocampal volume loss is affected by antipsychotic medication. Indeed, treatment with olanzapine and risperidone has been associated with larger hippocampal volumes in patients with schizophrenia as compared to those treated with haloperidol in a cross-sectional study,[9] but this finding was not replicated in another study with chronically ill patients.[10] In addition, 2 follow-up studies with short scan intervals (both less than a year) found no relationship between type of antipsychotic medication and hippocampal volume change.[11,12]

Earlier, we reported on excessive global brain volume change in patients with schizophrenia relative to healthy individuals.[13] In the current study, we used the same data set to compare age-related hippocampal volume change between 96 patients with schizophrenia and 113 healthy individuals. Furthermore, the relationship between cumulative dose of antipsychotic medication during the scan interval and hippocampal volume change in patients was investigated.

## METHOD

### Subjects

A 5-year follow-up magnetic resonance imaging (MRI) study was carried out between 1995 and 2003, including patients with schizophrenia and healthy comparison subjects. At baseline (T0), 159 patients with schizophrenia (112 male/47 female) and 158 healthy individuals (106 male/52 female) were included.[14] A total of 96 patients with schizophrenia (70 male/26 female) and 113 healthy comparison subjects (76 male/37 female) completed the longitudinal study and were rescanned after an interval of 5 years (T5).[13,15] The study was approved by the Human Ethics Committee of the University Medical Center Utrecht. Written informed consent was obtained from all subjects.

Criteria for inclusion in the study and clinical assessment were discussed previously[13–15] and will be described only briefly. At baseline measurement, subjects with a major medical or neurologic illness, including migraine, epilepsy, hypertension, cardiac disease, diabetes mellitus, endocrine disorders, cerebrovascular disease, alcohol abuse, or other drug dependence in the 6 months before entry in the study; head trauma in the past; or an IQ below 80 were excluded from this study. Both at baseline and at follow-up, the presence or absence of psychopathology was established using the Comprehensive Assessment of Symptoms and History

(CASH)[16] and was assessed by 2 independent raters. Patients gave permission to contact their treating physician or nurse for further information, and medical records were used when necessary. In the instance that the information provided by the patient, medical records, treating physician, or nurse was not reliable, the patient was excluded from the analysis.

Diagnostic consensus was achieved in the presence of a psychiatrist. All patients met *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (*DSM-IV*) criteria for schizophrenia or schizophreniform disorder at time of first measurement; those with schizophreniform disorder were reassessed and met the criteria for a diagnosis of schizophrenia after 1 year of illness. At follow-up, all patients met criteria for schizophrenia except 4 who received a diagnosis of schizoaffective disorder. Severity of illness was measured using the Positive and Negative Syndrome Scale (PANSS).[17] Outcome at follow-up was measured using the Camberwell Assessment of Need (CAN; sum of all relevant needs as rated by the treating physician divided by the number of relevant needs)[18] and Global Assessment of Functioning (GAF)[19] scales. Age at onset of illness was defined as the first time the patients experienced psychotic symptoms, as obtained from the CASH interview.[16] Duration of illness was defined as the time between age at onset of illness and age at first MRI scan. Information on number of hospitalizations and total duration of hospitalization during the scan interval was obtained from the CASH interview[16] and the patient's medical records.

To calculate the cumulative dosage of typical antipsychotics during the scan interval, a table from the Dutch National Health Service[20] was used to derive the haloperidol equivalents (similar to the guidelines from the American Psychiatric Association).[21] For atypical antipsychotics, the respective pharmaceutical companies suggested conversion rates into haloperidol equivalents (clozapine, 40:1; olanzapine, 2.5:1; risperidone, 1:1; sulpiride, 170:1; quetiapine, 50:1; and sertindole, 2:1). No reliable information on medication intake during the scan interval was available for 6 patients. Ten patients had been taking typical antipsychotic medication exclusively, and 27 patients had been taking atypical antipsychotic medication exclusively over the entire 5-year period. Forty-three patients switched between typical and atypical medication during the scan interval. Thirty of these 43 patients switched from typical to atypical antipsychotic medication, 1 patient from atypical to typical antipsychotic medication, and 12 patients changed several times between the 2 types of drugs during the 5-year interval. Clozapine and olanzapine were the types of atypical antipsychotics most often prescribed.

All healthy comparison subjects met Structured Interview for DSM-IV Personality[22] criteria for "never mentally ill" and had no first-degree family members with a psychotic illness. The comparison subjects were matched for age, sex, handedness, height, socioeconomic status of their parents (expressed as the highest level of education completed by 1 of the parents), and scan interval.

**Table 1. Segmentation Procedure of the Hippocampus**

| Border | |
|---|---|
| Anterior | The first coronal slice in which the characteristic oval shape of the mamillary bodies is visible. |
| Posterior | The last slice to be segmented; the slice before the slice in which the fornix forms a continuous tract for the first time. |
| Superior | The inferior horn of the lateral ventricle. |
| Inferior/Medial | The surrounding white matter; the subicular complex and the uncal sulcus are included in this segment. |

### Brain Imaging

Magnetic resonance imaging brain scans at baseline and follow-up were acquired on a Philips NT scanner operating at 1.5T (Philips Medical Systems, Best, The Netherlands) using the identical scanning protocol for all subjects on both measurements. Details of the MRI acquisition protocol and processing of the images have been presented before.[23–25] Briefly summarized, quantitative assessments of intracranial, cerebrum (gray and white matter of the cerebrum, excluding the cerebellum and brainstem), lateral and third ventricles, and peripheral cerebrospinal fluid volumes were performed on the basis of histogram analyses and series of mathematical morphological operators to connect all voxels of interest. The hippocampus was manually segmented using Display imaging software (http://www.bic.mni.mcgill.ca/software/Display/) according to a fixed set of rules. This hippocampus segmentation procedure has been published previously.[26–28] In short, the hippocampus is part of the parahippocampal gyrus, but it is segmented separately. Segmentation is done in coronal slices, from anterior to posterior (Table 1). Every segment was checked in all dimensions after the initial segmentation. To be certain that there were no voxels in the hippocampal segment that were actually part of the cerebrospinal fluid in the temporal horns, the segment was multiplied with the cerebrum segment.

The interrater reliability of the volume measurements between 3 trained raters (P.C.M.P.K., F.K., and J.J.), determined by the intraclass correlation coefficient (ICC)[29] in 13 brains for the left and right hippocampus, was at least 0.85 or higher (range, 0.85–0.95). Intrarater reliabilities for left and right hippocampus were 0.85 or higher (range, 0.85–0.96).

Due to poor quality of the scans, no hippocampal segmentations were obtained from 6 patients with schizophrenia (5 at baseline) and 2 healthy controls (both at baseline), resulting in hippocampal volumes for 153 patients with schizophrenia and 156 healthy controls at baseline, of which 95 patients with schizophrenia and 113 healthy controls had a follow-up measurement.

### Statistical Analysis

Data were checked for outliers, extreme values, and the normality of the distribution. Except for the different medication variables, all variables were normally distributed. Nonparametric testing was used in the instance that

the medication variables were included into the analysis. All analyses were performed for left, right, and total hippocampal volume (change).

Hippocampal volume change per year was calculated by subtracting baseline volume from follow-up volume, dividing it by the duration of the scan interval in years ([T5 – T0]/interval) and is thus expressed as milliliter change per year.

Correlation analyses showed that hippocampal volume change was significantly associated with hippocampal volume at baseline ($r = -0.335$, $P < .0001$) and change in cerebral brain volume ($r = 0.305$, $P < .0001$). Linear regression was used to correct hippocampal volume change per year for hippocampal volume at baseline, change in cerebral brain volume per year, and sex and age at baseline, and unstandardized residuals were saved (ie, further referred to as corrected hippocampal volume change). In addition, linear regression was used to correct hippocampal volume at baseline for age at baseline, and sex and cerebral brain volume at baseline, and unstandardized residuals were saved (ie, further referred to as corrected baseline hippocampal volume).

### Group Differences

First, we used a general linear model univariate analysis to detect cross-sectional group differences, using age at baseline, sex, and cerebral brain volume as covariates. This analysis was performed on the total baseline sample ($N_{pt} = 153$ patients with schizophrenia and $N_{nc} = 158$ controls) and on the subsample of only those subjects that participated at follow-up ($n_{pt} = 95$ patients with schizophrenia and $n_{nc} = 113$ controls). Moreover, corrected hippocampal volume change was compared between the groups.

Because we were particularly interested in the relationship between age and hippocampal volume change in both groups in this study, a regression analysis in the form of a locally weighted running-line smoother[30,31] was used to obtain the dependence of volume changes on age (see also reference 13). Software for these analyses was developed in-house (available from the authors on request). Fits with different *df* were calculated for each group to find the one that described the data best. Standard error bands were calculated to show the age at which volume change differed significantly between patients with schizophrenia and healthy subjects.

The analyses were done on corrected and uncorrected hippocampal volume change, both with and without correcting for sex. The results from these analyses were similar; therefore, the findings of the uncorrected volume changes per year are reported here.

### Relationship With Clinical Variables

In the patients with schizophrenia group only, Pearson and Spearman rank correlations were calculated between corrected hippocampal volume change and (1) medication intake (cumulative intake of typical antipsychotic medication in haloperidol equivalents, atypical antipsychotic medication in haloperidol equivalents per year during the scan interval [haloperidol equivalents/scan interval], and clozapine and olanzapine in milligrams per year during the scan interval [milligrams/scan interval]) and (2) outcome (ie, GAF score at follow-up, CAN score [a square-root transformation was performed to create a normal distribution of the data] at follow-up, number of hospitalizations and total duration of hospitalization during the scan interval, and scores on the positive, negative, and general symptom scales of the PANSS at follow-up).

A 2-tailed α level of .05 was used to determine significance of the effect.

### Selection Bias at Follow-Up

At baseline, the patients with schizophrenia included at follow-up were younger and had a shorter duration of illness, fewer negative symptoms, and larger volumes of cerebral (gray) matter than those who did not complete the follow-up (for further details, see reference 15). Moreover, the number of years of education was significantly lower in patients with schizophrenia who participated only at baseline compared with those included at follow-up. A linear regression analysis was performed to compare corrected baseline hippocampal volume between patients with schizophrenia who participated at follow-up and patients with schizophrenia who did not. This analysis was repeated to investigate the confounding effects of negative symptoms, duration of illness, or years of education.

## RESULTS

### Group Differences

For demographic information at baseline and follow-up, see Table 2. Mean and SD hippocampal volumes at baseline and follow-up are presented in Table 3.

In the total baseline sample ($N_{pt} = 153$; $N_{nc} = 156$), patients with schizophrenia had significantly smaller bilateral hippocampus volumes compared to healthy controls after correction for age, sex, and cerebral brain volume (left: $F = 8.205$, $P = .004$; right: $F = 5.49$, $P = .02$; total: $F = 7.81$, $P = .006$). However, when including only those subjects who participated at follow-up, the difference in baseline hippocampus volume between patients and controls was no longer significant (left: $F = 0.665$, $P = .416$; right: $F = 1.863$, $P = .174$; total: $F = 1.386$, $P = .24$). Moreover, at follow-up, no significant difference in hippocampal volume between the groups was present (left: $F = 0.071$, $P = .79$; right: $F = 1.21$, $P = .291$; total: $F = 0.182$, $P = .67$)

Finally, no differences were found in the rate of volume change in the patients with schizophrenia group compared to the control group (left: $F = 1.131$, $P = .289$; right: $F = 0.143$, $P = .705$; total: $F = 0.229$, $P = .633$).

Our main interest concerned the association between age and hippocampal volume change and possible differences in this relationship between patients with schizophrenia and healthy individuals. Healthy controls showed a linear relationship between hippocampal volume change and

**Table 2. Demographic and Clinical Variables of All Subjects at Baseline and Follow-Up**

| | Patients With Schizophrenia | | | Healthy Comparison Subjects | | |
|---|---|---|---|---|---|---|
| | | Patients Included at Follow-Up (n = 95[a]) | | | Patients Included at Follow-Up (n = 113) | |
| Variable | Total Baseline (n = 153) | Baseline | Follow-Up | Total Baseline (n = 156) | Baseline | Follow-Up |
| Sex, male/female, n/n | 108/45 | 69/26 | 69/26 | 105/51 | 76/37 | 76/37 |
| Age, mean (SD), y | 34.82 (12.31) | 32.16 (11.14) | 36.98 (11.25) | 37.33 (13.87) | 35.28 (12.25) | 40.22 (12.21) |
| Range, y | 16.88–67.53 | 16.88–56.25 | 21.32–61.25 | 16.75–67.79 | 16.75–56.27 | 21.97–61.54 |
| Height, mean (SD), cm | 176.27 (9.30) | 176.69 (9.5) | | 178.05 (8.7) | 178.4 (8.4) | |
| Handedness, right-handed/left-handed/both, n/n/n | 131/19/3 | 82/10/3 | | 131/23/2 | 96/15/2 | |
| Level of education, mean (SD), y[b] | 10.81 (2.95) | 12.03 (2.77) | | 12.07 (2.97) | 12.81 (2.57) | |
| Parental level of education, y[c] | 10.67 (3.29) | 11.08 (3.08) | | 10.66 (2.87) | 10.92 (2.69) | |
| Follow-up duration, mean (SD), y | | | 4.83 (0.55) | | | 4.94 (0.32) |
| Range | | | 3.48–6.34 | | | 4.15–5.71 |
| Age at onset of illness, mean (SD), y | 20.97 (5.36) | 21.29 (5.43) | | | | |
| Range | 9–36 | 9–36 | | | | |
| Duration of illness at baseline, mean (SD), y | 13.94 (12.28) | 10.86 (10.25) | | | | |
| Range (n = 152)[d] | 0.40–51.53 | 0.40–36.25 | | | | |
| < 1 y | 10 | 10 | | | | |
| 1–2 y | 16 | 9 | | | | |
| 2–5 y | 31 | 23 | | | | |
| 5–10 y | 18 | 15 | | | | |
| 10–20 y | 29 | 18 | | | | |
| > 20 y | 48 | 20 | | | | |
| Positive and Negative Syndrome Scale score, mean (SD) | | | | | | |
| Negative symptoms | 18.47 (5.65) | 17.78 (5.52) | 13.22 (6.03) | | | |
| Positive symptoms | 17.04 (5.61) | 16.87 (5.83) | 13.74 (5.23) | | | |
| General psychopathology | 36.24 (9.33) | 35.74 (8.36) | 26.75 (8.32) | | | |
| Global Assessment of Functioning score at follow-up, mean (SD) | | | 52.62 (17.20) | | | |
| Range (n = 93) | | | 11–90 | | | |
| Cumulative medication intake per year during the scan interval, mean (SD)[e] | | | | | | |
| Only typical antipsychotic medication (n = 10, HEQ) | | | 1828 (1238) | | | |
| Only atypical antipsychotic medication (n = 27, HEQ) | | | 1403 (1031) | | | |
| Patients who switched and used among others[f] | | | | | | |
| Typical (n = 43, HEQ) | | | 366 (451) | | | |
| Atypical (n = 36, HEQ) | | | 789 (693) | | | |

[a]Hippocampal volume was not obtained from 1 patient due to poor scan quality.
[b]Level of education was significantly lower in patients than in comparison subjects ($F = 15.511$; $P < .001$). Level of education was also significantly lower in patients who participated only at baseline compared with patients included at follow-up ($F = 4.292$; $P = .04$).
[c]Used to determine socioeconomic status; the highest level of education completed by 1 parent.
[d]Duration of illness was significantly longer in patients who participated only at baseline compared with patients included at follow-up ($F = 17.736$; $P < .001$). Information not available for 1 patient.
[e]Cumulative typical and atypical antipsychotic medication intakes are in haloperidol equivalents per year during the scan interval. Cumulative olanzapine intake is in milligrams per year during the scan interval.
[f]During the scan interval, 52 patients switched between at least 2 of typical antipsychotics and atypical antipsychotics. For example, 43 of these patients used typical antipsychotic medication at some point during the scan interval, but have also been taking atypical antipsychotics.
Abbreviation: HEQ = haloperidol equivalent.

age, representing a larger decrease of hippocampal volume with increasing age ($df = 2$; Figure 1 in black). Around the age of 20 years, very little hippocampal volume change was present, while around the age of 45 years, the decrease was 0.1 mL/y), showing a further decrease to approximately 0.15 mL/y around the age of 55 years. In contrast, hippocampal volume loss in patients with schizophrenia remained stable across the entire age range ($df = 1$; Figure 1 in gray), decreasing approximately 0.05 mL/y. The slopes of patients with schizophrenia and healthy controls were significantly different before the age of 26 years (nonoverlapping SE bands), showing increased volume loss in patients with schizophrenia relative to controls; conversely, after the age of 40 years, the slopes showed significant progressive volume loss in controls relative to patients with schizophrenia.

Results for age-related volume change in the left and right hippocampus were similar to those found for total hippocampal volume change.

### Relationship With Clinical Variables

Correlations between unstandardized residuals of corrected hippocampal volume change (corrected for baseline hippocampal volume, change in cerebral volume, sex, and age at baseline) and cumulative dose of antipsychotic medication per year were calculated. A significant positive association was found between hippocampal volume change and cumulative intake of atypical antipsychotics per year during the scan interval ($n = 49$, $\rho = 0.31$, $P = .028$; Figure 2A); higher exposure to atypical antipsychotics was associated with less decrease in hippocampal volume. Olanzapine,

**Table 3. Hippocampal Volumes at Baseline and Follow-Up of Patients With Schizophrenia and Comparison Subjects[a]**

| | Patients With Schizophrenia | | | Healthy Comparison Subjects | | |
|---|---|---|---|---|---|---|
| | | Patients Included at Follow-Up (n = 95[b]) | | | Patients Included at Follow-Up (n = 113) | |
| Volume, mean (SD), mL | Total Baseline (n = 153) | Baseline | Follow-Up | Total Baseline (n = 156) | Baseline | Follow-Up |
| Left hippocampus | 3.57 (0.57)[c] | 3.66 (0.52) | 3.54 (0.55) | 3.77 (0.57)[c] | 3.75 (0.57) | 3.57 (0.58) |
| Right hippocampus | 3.57 (0.58)[d] | 3.61 (0.58) | 3.50 (0.55) | 3.76 (0.59)[d] | 3.77 (0.60) | 3.63 (0.62) |
| Total hippocampus | 7.15 (1.09)[e] | 7.27 (1.04) | 7.05 (1.03) | 7.53 (1.09)[e] | 7.51 (1.11) | 7.20 (1.14) |

[a]Patients in the total baseline sample showed bilateral smaller corrected baseline hippocampal volumes compared to healthy comparison subjects at baseline.
[b]Hippocampal volume was not obtained from 1 patient due to poor scan quality.
[c]$F = 8.205$; $P = .004$.
[d]$F = 5.49$; $P = .02$.
[e]$F = 7.81$; $P = .006$.

in particular, showed a positive association between atypical antipsychotic exposure and hippocampal volume change that reached trend-level significance (n = 37, ρ = 0.32, $P = .056$). Moreover, a negative correlation between cumulative intake of typical antipsychotics and hippocampal volume change (n = 51, ρ = –0.27, $P = .058$; Figure 2B) was significant at trend level, indicating that a larger dose of typical antipsychotics during the scan interval was correlated with a larger decrease in hippocampal volume. One patient, who was prescribed a larger dose of typical antipsychotics compared to all other patients, was excluded from the correlation analysis. This did not change our findings (n = 52, ρ = –0.26, $P = .062$). After Bonferroni correction for multiple comparisons, our findings were no longer significant.

No significant differences were found between "good" and "poor" outcome patients with schizophrenia (as defined by GAF[19] score at follow-up). In addition, no significant correlations were found between scores on the negative, positive, or general symptom scales of the PANSS,[17] CAN[18] scores at follow-up, number and total duration of hospitalizations during the interval, and corrected hippocampal volume change at the .05 significance level.

### Selection Bias at Follow-Up

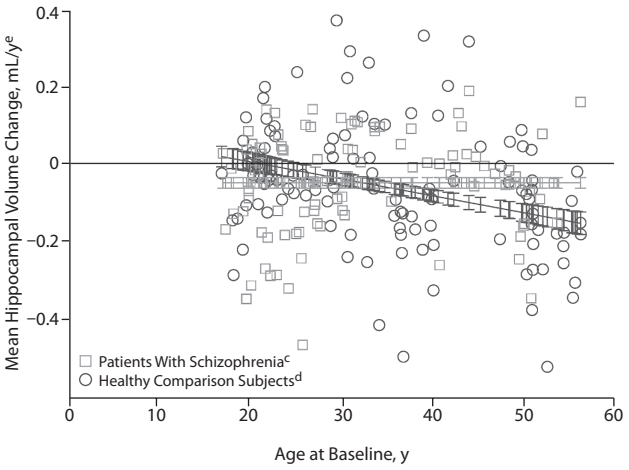
No significant differences were found between corrected baseline hippocampal volumes between patients with schizophrenia who participated at follow-up and those who did not ($F = 2.062$, $P = .153$). Moreover, adding level of negative symptoms ($F = 1.359$; $P = .246$), duration of illness ($F = 1.002$; $P = .318$), or years of education of parent ($F = 1.684$; $P = .196$) as covariates did not change this finding.

## DISCUSSION

This 5-year follow-up study compared age-related hippocampal volume change in 95 patients with schizophrenia relative to 113 healthy control subjects. The main finding is that the trajectory of hippocampal volume change over time differs between patients with schizophrenia and healthy individuals. Before the age of 26 years, patients with schizophrenia demonstrated a pattern of larger hippocampal volume loss relative to healthy controls, but thereafter, patients with schizophrenia did not show excessive volume loss when compared with healthy controls. In fact, after the age of 40 years, healthy individuals showed a larger volume loss relative to the patients with schizophrenia, suggesting that progressive brain abnormalities are present (only) in the early course of the disease.

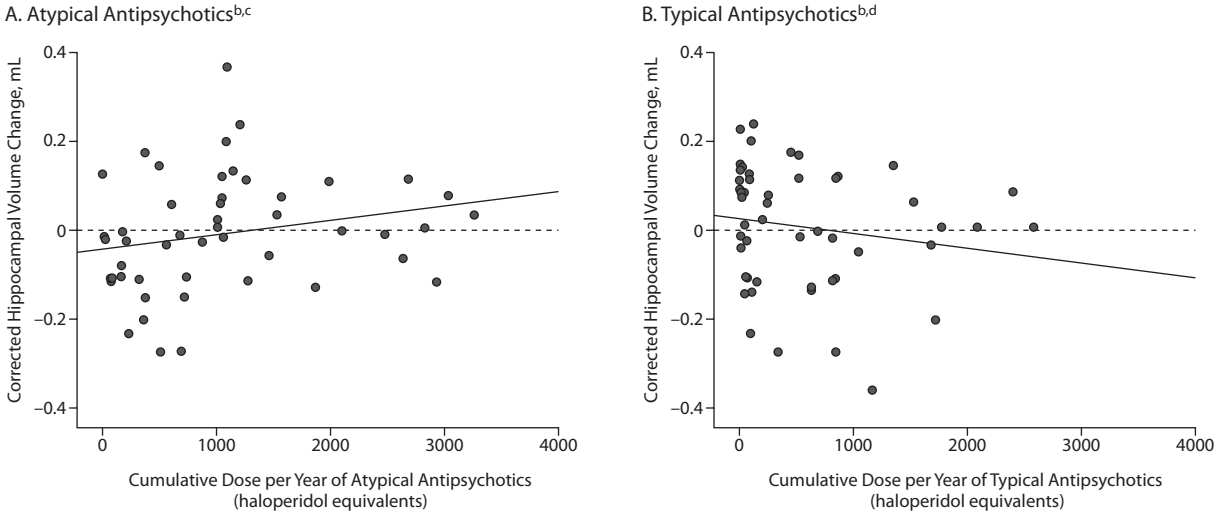
Our results are consistent with those of cross-sectional studies reporting decreased hippocampal volumes in patients with first-episode schizophrenia,[32] with effect sizes twice as large as those found in chronically ill patients.[1] One may speculate that this early volume loss is the result of increased (psychological) stress that accompanies the onset of psychosis, since it has been demonstrated that increased levels of circulating cortisol have been associated with atrophy and loss of neurons in the hippocampus.[33–36]

**Figure 1. Age-Related Trajectory of Hippocampal Volume Change in Patients With Schizophrenia and Healthy Comparison Subjects[a,b]**




[a]Correction for change in cerebral brain volume, hippocampal volume at baseline, and sex did not change the results.
[b]The bars in the figure represent the standard error bands determined by the regression analysis in the form of a locally weighted running-line smoother. Nonoverlapping standard error bands indicate a significant difference in the slopes of patients with schizophrenia and healthy individuals.
[c]Linear $df = 1$.
[d]Linear $df = 2$.
[e]The y-axis represents the mean volume change per year during the interval that started at this particular age.

**Figure 2. Association Between Corrected Hippocampal Volume Change and Cumulative Dose of Atypical and Typical Antipsychotics[a]**




[a]One patient who was prescribed a large dose of typical antipsychotics compared to all other patients was excluded from the analysis.
[b]Haloperidol equivalents.
[c]Higher exposure to atypical antipsychotic medication was related to smaller decrease or even small increase of hippocampal volume over time.
[d]Higher cumulative dose of typical antipsychotic medication was related to larger decrease of hippocampal volume over time (at trend level).

Interestingly, individuals at high risk for psychosis who subsequently developed frank psychosis display higher levels of anxiety and depressive symptoms than those who do not go on to develop psychosis.[37] However, brain changes during the period of transition to illness are inconsistent.[38] Because depressive symptoms and depression are highly prevalent in schizophrenia[39] and have been related to decreased hippocampal volume,[40,41] these factors could be potential confounders. Although in our sample a small number of patients showed minor depressive symptoms (as measured with the depressive scale of the PANSS) and were treated with antidepressants, no significantly different hippocampal volume (change) was found compared to those solely treated with antipsychotic medication.

In contrast to the progressive hippocampal volume loss before the age of 26 years in patients with schizophrenia, healthy individuals demonstrated a progressive volume loss after the age of 40 years relative to the patients with schizophrenia group. The linearly increasing hippocampal volume loss as age increases is in line with earlier findings in normal aging demonstrating accelerated hippocampal volume loss in later life.[42,43]

Antipsychotic medication intake appears to be an important confounder when investigating hippocampal volume over time. A significant positive association was found between cumulative intake of atypical antipsychotics, olanzapine in particular, and hippocampal volume change. Patients with schizophrenia who were exposed for a longer period or received a higher dose of atypical antipsychotics over time showed less decrease or even small increases in hippocampal volume. In contrast, a negative correlation (although only significant at trend level) was found between cumulative intake of typical antipsychotics and hippocampal volume change, suggesting that patients who received more typical antipsychotic medication during the scan interval showed larger decreases in hippocampal volume. Although our findings indicate a positive association between atypical antipsychotic medication intake and hippocampal volume change, suggesting possible neuroprotective properties of atypical antipsychotics similar to those found in previous reports,[44,45] these findings should be interpreted with caution, since many of the patients currently receiving atypical medication may have been prescribed typical medication at an earlier stage of their illness.

Evidence from animal studies indicates that atypical antipsychotics, such as quetiapine and olanzapine, increase neurogenesis in the hippocampus[46–48] (but see Schmitt et al[49]). Moreover, olanzapine and quetiapine have been associated with increased hippocampal cell proliferation and prevention of brain-derived neurotrophic factor (BDNF) decrease compared to typical antipsychotics such as haloperidol.[50–52] Interestingly, BDNF regulates neuronal cell survival, differentiation, synaptic strength, and morphology,[53] and emerging evidence suggests that several polymorphisms of the BDNF gene play a role in several neuropsychiatric disorders, including schizophrenia.[54]

Although hippocampal volume was significantly smaller in the (larger) baseline schizophrenia sample than in the controls, the difference no longer reached significance after including only those subjects who participated at follow-up. Inspection of Table 3 indeed indicates that hippocampus volume in the total sample of controls and the subsample of control subjects who participated at follow-up is almost similar, while for the patients with schizophrenia, it is not. Patients with schizophrenia who participated at follow-up showed a larger baseline hippocampal volume than patients



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who participated only at baseline; although this difference was not significant, this might suggest a selection bias in our follow-up sample. Indeed, as was presented earlier,[15] those patients that were lost for follow-up were older, hence had a longer illness duration, showed more negative symptoms, and had smaller cerebral gray matter volume at baseline. Moreover, those patients included at follow-up had a higher level of education compared to those lost for follow-up. However, these dissimilarities could not explain the lack of difference in baseline hippocampal volume between included and excluded patients with schizophrenia.

Several other limitations have to be taken into consideration when interpreting these findings. Most patients with schizophrenia changed medication during the scan interval, making it difficult to reliably investigate the specific effects of different types of antipsychotics. Only 10 patients were exclusively taking olanzapine during the scan interval; therefore, it cannot be ruled out that the protective effect can be explained by the release of exposure to typical antipsychotics. Moreover, it should be noted that patients with schizophrenia differed in the amount of medication they had used prior to inclusion in the study, while reliable information on their lifetime cumulative medication use was not available.

Similar to Whitworth et al,[8] we found no association between hippocampal volume change and clinical variables such as symptom and outcome measurements at follow-up. However, it must be noted that CAN and GAF scores were not available at baseline. Therefore, whether improvement in daily life functioning between baseline and follow-up was associated with hippocampal volume change could not be assessed.

In summary, the age-related trajectories of hippocampal volume change differ significantly between patients with schizophrenia and healthy control subjects, with patients with schizophrenia showing an excessive volume decrease in the early course of the illness. In contrast, after the age of 40 years, the control group showed a progressive decrease of hippocampal volume with increasing age relative to the patients with schizophrenia. Speculatively, these differences could be taken to suggest that the high levels of stress that accompany the onset of psychosis result in decreases in hippocampal volumes. Moreover, our findings suggest a differential influence of typical and atypical antipsychotic medication, since a larger dose of atypical antipsychotic medication during the interval was related to a smaller decrease of hippocampal volume, suggestive of neuroprotective effects of atypical antipsychotic medication.

***Drug names:*** clozapine (FazaClo, Clozaril, and others), haloperidol (Haldol and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal and others).

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***Potential conflicts of interest:*** None reported.
***Funding/support:*** None reported.
***Previous presentation:*** Presented as a poster at the International Congress on Schizophrenia Research, March 28–April 1, 2007, Colorado Springs, Colorado, and at the Human Brain Mapping conference, June 10–14, 2007, Chicago, Illinois.

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