Table DS1 Characteristics of the participants

	Mean (SD)		Statistic	p Value
	SZ (n = 51)	Control (n = 49)		
Demographics				
Age	48.9 (17.9)	52.8 (17.2)	$t(98) = 1.12$	0.268
Gender				
Female	23	23	$\chi2(1) = .034$	0.506
Education	11.4 (5.2)	13.3 (4.5)	$t(90) = 1.88$	0.063
MRI volumes (cc)				
Right Hippocampus	2.4 (0.4)	2.6 (0.3)	$t(98) = 1.58$	0.117
Left Hippocampus	2.8 (0.4)	2.9 (0.4)	$t(98) = 1.78$	0.078
ICV	1412.3 (238.1)	1489.0 (182.9)	$t(98) = 1.68$	0.096
Cognition and function				
Vocabulary	37.2 (9.6)	46.1 (8.5)	$t(91) = 4.70$	< 0.001
RAVLT-Total	40.2 (11.1)	49.9 (9.9)	$t(91) = 4.48$	< 0.001
RAVLT-Delayed	7.7 (3.3)	10.5 (2.8)	$t(91) = 4.39$	< 0.001
Elderly subsample				
MMSE	24.8 (6.5)	29.6 (0.6)	$t(49) = 4.09$	< 0.001
FAQ	8.3 (10.6)	0 (0)	$t(48) = 4.30$	< 0.001
Clinical				
PANSS (total)	58.3 (18.0)	NA		
PANSS (P)	10.1 (4.0)			
PANSS (N)	16.2 (7.9)			
PANSS (G)	32.0 (9.5)			
PANSS (total)	58.3 (18.0)	NA		
Age of onset	25.94 (8.4)			
Length of illness (ys)	21.4 (15.8)			
Hospitalizations	2.5 (1.9)			
Treatment[a]		NA		
Clozapine	13			
Other atypical	45			
Dose (CPZ equiv., mg)	241.6 (148.1)	NA		

SZ, Schizophrenia; HC, Healthy control; ICV, Intracranial volume; PANSS-P, Positive and Negative Syndrome Scale-Positive score; PANSS-N, Positive and Negative Syndrome Scale-Negative score; PANSS-G, Positive and Negative Syndrome Scale-General score; RAVLT-T, Rey Auditory Verbal Learning Test-Total score; RAVLT-D, Rey Auditory Verbal Learning Test-Delayed score; MMSE, Mini Mental State Evaluation. a Other atypical were aripiprazole (7), quetiapine (6), olanzapine (17), risperidone (13), paliperidone (2). No patients were on typical antipsychotics. Five patients were on two antipsychotics.
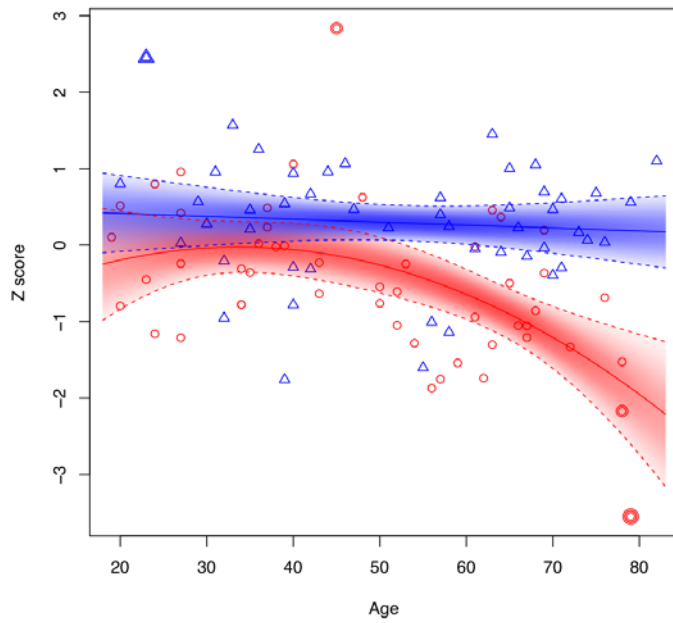
Fig. DS1 Accelerating decline in hippocampal volume in older patients with schizophrenia. Hippocampal volume as a function of age in schizophrenia and healthy control group (Z scores normalised by ICV and adjusted by gender). The blue line corresponds to the best model (linear) for the healthy control data, while the shaded area corresponds to the 95% confidence interval for the fit. The red line corresponds to the best model (quadratic) for the association between age and hippocampal volume in schizophrenia. Extreme measurements have been identified by double marks (those beyond two standard deviations from the mean) or triple marks (3 standard deviations) as potential outliers (see below).
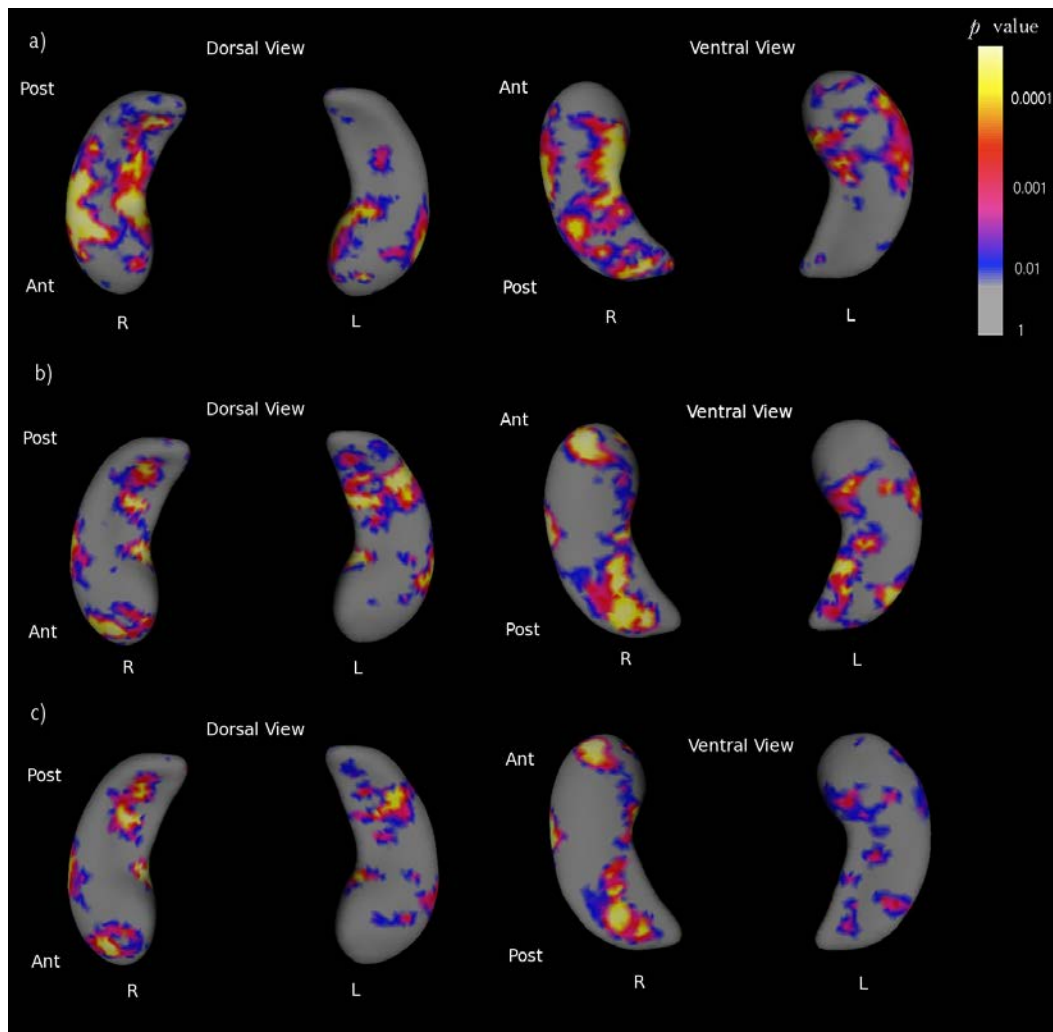
Fig. DS2 Hippocampal shape analysis: (a) areas with steeper hippocampal thickness reduction with age in schizophrenia relative to controls (group×age interaction); (b) areas where thickness reduction is associated with lower Mini-Mental State Examination scores; (c) areas where thickness reduction is associated with Functional Activities Questionnaire (FAQ) scores (worse socio-occupational function). All patterns were significant when corrected for multiple comparisons by a permutation-based procedure (all $P<0.05$ corrected) except for FAQ and left hippocampus (P=0.066). Dorsal view: from top, right hippocampus on the left; ventral view: from bottom, right hippocampus on the left. Ant, anterior; L, left; Post, posterior; R, right.

Method: Assessing the sensitivity to outliers of the relationship between age, diagnosis of schizophrenia and hippocampal volume

A sensitivity analysis was conducted to assess whether the main findings of the paper were robust to the deletion from the sample of the most extreme measurements. Such extreme measurements can exert high leverage in the fitting of the model to the data. Outliers were operationally defined as those measurements beyond 2 standard deviations from the mean (3 patients and 1 control, see Fig. DS1).

Excluding these 4 measurements did not affect the finding of steeper hippocampal reduction with age in patients with schizophrenia relative to controls (age by group interaction, F=5.57, df1=1,df2=91, P=0.020). However, the quadratic model was no longer a significantly better fit to the patient data than the linear one (ANOVA comparing linear and quadratic model: F=0.26, df1=1,df2=44, P=0.616).

Employing a more restrictive definition of outlier (measurements beyond 3 standard deviations from the mean, only 1 schizophrenia participant in our sample, see Fig. DS1) resulted in the same conclusions (age by group interaction, F=4.50, df1=1,df2=94, P=0.037; ANOVA comparing linear and quadratic model: F=2.50, df1=1,df2=46, P=0.120).

Results: Analysis of years of education, age and diagnosis

Examining the effects of age is always potentially conditional on cohort effects, in the sense that relationship between variables can change across time periods, due, for instance, to societal change (Goldstein H. Age, period and cohort effects – a confounded confusion. *J Appl Stat* 1979; **6**: 19–24). Confounding through cohort effect could have occurred in our sample if the changes observed in hippocampal volume with age were due not to the effects of chronic illness, but to differential (increased) effects in patients more than in controls of another risk factor for hippocampal atrophy in older relative to younger participants. A potential confounder through cohort effects is early economic deprivation, with very different patterns of deprivation in the first half of the 20th century relative to the second half. Particularly in Spain, the second of these periods was characterised by rapid industrialisation and improvement in wealth and public health.

Length of education is a recognised marker of socioeconomic status, established in childhood and early adulthood (generally completed by age 25) and stable afterwards (i.e. it is not modified by the later effects of chronic illness, such as schizophrenia.

Possible cohort effects on length of education were analysed, as a marker of early deprivation, as well as a known protective factor against hippocampal atrophy in its own right. A linear model was fitted with years of education as the dependent variable, and age, diagnostic group (schizophrenia or healthy control) and their interaction as independent variables. If deprivation is a confounder due to cohort effects (differential effects in patients and controls depending on their age), there would be an expectation of a significant age by diagnosis interaction effect, with older patients with schizophrenia having reduced education after accounting for the main effects of age and diagnosis.

In this analysis there was a significant main effect of schizophrenia diagnosis with a reduction in years of education for patients relative to controls (F(1,88)=4.01, P=0.048) and significant main effect of age with less education in older relative to younger participants irrespective of diagnosis (F(1,88)=7.94, P=0.006). The interaction between

age and diagnosis was significant (F(1,88)=6.33, P=0.014). However, this interaction effect was in the opposite direction than would have been expected should this confounder explain the findings, with older patients with schizophrenia having increased education relative to what would be expected given age and diagnosis. As length of education is a protective factor against hippocampal atrophy, this effect would, if anything, detract to the significance of the main findings of the paper.

Given these differences in education, we repeated the analyses of the effects of age and diagnostic group on hippocampal volume, while adjusting for years of education. The inclusion of years of education did not alter our findings (group-by-age interaction without adjusting for education: F(1,95)=6.57, P=0.012; after adjusting for education F(1,87)=6.14, P=0.015). There was no independent effect of years of education on hippocampal volume in this sample (F(1,87)=0.54, P=0.464).