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Hippocampal CA1 deformity is related to symptom severity and antipsychotic dosage in schizophrenia

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Abnormalities of the hippocampus are intricately involved in the pathophysiology of schizophrenia. Hippocampal volume decrease is present at disease onset and has mainly been observed in the anterior and posterior part of the hippocampus. Nevertheless, an association between regionally specific hippocampal shape deformities putatively affecting a pathophysiologically crucial region, i.e. cornu ammonis field 1 (CA1), and symptomatology as well as required maintenance medication has not been observed. The aim of this study was to characterize the relationship between CA1-specific hippocampal surface deformations and symptom severity. Furthermore, we aimed to explore whether such specific morphological hippocampus abnormalities statistically predict the maintenance dosage of antipsychotic medication. Hippocampal shape and volume were determined by manual segmentation of high resolution, whole brain, three-dimensional structural magnetic resonance imaging scans. Associations between hippocampal volume, specific shape deformities in CA1, and positive and negative symptoms were assessed in 32 patients with schizophrenia and compared with 34 healthy control subjects. In addition to volume reductions of the left hippocampus, patients with schizophrenia displayed specific shape deformities in the left anterior and posterior CA1 subfield. Overall, the severity of positive symptoms was closely associated to these morphological deformities, specifically delusions and hallucinations. In addition, CA1 deformity was linked to the required antipsychotic dosage. Findings were replicated in a second, independent sample. Hippocampal CA1 deformity, possibly reflecting shrinkage, might result from a specific hyperactivity, leading to a circumscribed volume loss. Owing to its physiological function, deficits in CA1 may be directly involved in the pathogenesis of hallucinations and delusions, core symptoms in schizophrenia.

Keywords: chronic schizophrenia; hippocampus shape; CA1; positive symptoms; antipsychotic medication of maintenance
Abbreviations: CA1 = cornu ammonis field 1; PANSS = positive and negative syndrome scale

Introduction

In schizophrenia, alterations in the structure, function and physiology of the hippocampus have consistently been reported. Among those, hippocampal volume decreases are a robust finding in MRI studies using manual segmentation as well as in post-mortem studies (Bogerts, 1984, 1985, 1993*a*; DeLisi *et al*., 1988; Suddath *et al*., 1989; Breier *et al*., 1992; Heckers, 1997; Gur *et al*., 2000; Shenton *et al*., 2002).

Recent studies using computational image analysis methods investigated local and global differences in brain morphology that are potentially associated with neuropathological changes.

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In a series of studies, Csernansky *et al*. (1998) used high-dimensional deformation mapping showing hippocampal shape alterations in schizophrenia that were pronounced in anterior and lateral hippocampal regions (Haller *et al*., 1996; Csernansky *et al*., 1998, 2002; Wang *et al*., 2001). In contrast, using a shape representation technique, Shenton *et al*. (2002) failed to find overall differences in hippocampal shape between patients with schizophrenia and healthy control subjects. Szeszko *et al*. (2003) observed bilateral reductions of anterior hippocampal volumes in patients with first-episode schizophrenia. Accordingly, Narr *et al*. (2001, 2002) showed anterior and midbody structural hippocampus changes in schizophrenia. In these studies, volume deficits were particularly prominent in the left hemisphere of patients suffering from schizophrenia. Furthermore, Narr *et al*. (2004) reported volume reductions prominent in hippocampal regions that correspond to anterior and midbody cornu ammonis field 1 (CA1) and CA2 subfields in the left hemisphere of patients with first-episode schizophrenia.

The major efferent connections of the hippocampal formation to the cortex arise from the pyramidal cells of the CA1 and project either directly or via the subiculum to the cortex (Van Hoesen and Hyman, 1990). Pathology affecting the CA1 subfield results in a functional disconnection from its target areas. CA1 is specifically vulnerable to hypoxia (Duvernoy and Bourgouin, 1998; Harrison and Eastwood, 2001), a birth complication linked to schizophrenia. Furthermore, this hippocampal subregion appears sensitive to vascular cerebral insults or the hyperexcitation of glutamate receptors (Zola-Morgan *et al*., 1986; Duvernoy and Bourgouin, 1998). Dopamine hyperfunction, inhibiting glutamatergic (NMDA) *N*-methyl-D-aspartate input, dramatically reduces direct cortical input to CA1 via the perforant pathway. These effects of dopamine are blocked by typical antipsychotic drugs such as haloperidol, suggesting a link between dopaminergic activity and the CA1 field in schizophrenia-related pathophysiology (Otmakhova and Lisman, 2000; Lisman and Otmakhova, 2001).

Supporting the crucial role of hippocampal dysregulation, we recently showed that patients with schizophrenia exhibit a non-specific hyperactivity of the left hippocampus during a long-term memory task and that this hyperactivity is strongly related to positive symptom severity (Zierhut *et al*., 2010). Schobel *et al*. (2009) reported an increase in regional cerebral blood volume specifically in CA1. This abnormal cerebral blood volume increase is not only associated with positive symptoms but also predicts clinical progression from a prodromal state to psychosis.

To our knowledge, there is no study investigating the relationship between specific CA1 deformations—as a potential morphological marker—and symptom severity. We hypothesized that shape differences in terms of an inward deformation detectable in the CA1 region are closely associated to symptom severity. Furthermore, these shape differences in the CA subfield of patients with schizophrenia may statistically predict the required antipsychotic dosage, an indirect measure of symptom severity.

Therefore, we analysed hippocampal size and regional shape differences between patients with schizophrenia and healthy control subjects and related them to the patients' actual psychopathological state as well as the required antipsychotic dosage for maintenance treatment. The topographical distribution of the CA fields, dentate gyrus and subiculum is such that the CA1, CA2 and CA3 fields and subiculum are located at the surface of the hippocampal formation. Thus, we examined hippocampal surface deformations by using surface-based mesh modelling methods (Thompson *et al*., 1996*a*, *b*, 1997) to describe differences in hippocampal shape between diagnostic groups (Csernansky *et al*., 2002; Shenton *et al*., 2002). This mapping was then used to track regional differences in hippocampal surface parameters and local tissue distributions to characterize the regional specificity of hippocampal volume reductions in schizophrenia.

Materials and methods

Subjects

A clinically well-characterized group of 32 patients with paranoid schizophrenia (11 female, medicated with atypical antipsychotic drugs, no benzodiazepines, Table 1) (ICD-10 F20, no neuropsychiatric comorbidities) and 34 healthy volunteers (14 female) participated in this study. According to the structured clinical interview of the positive and negative syndrome scale (PANSS), all patients were mildly to moderately impaired (Table 1), and all patients were in a remitted state. Patients had on average an illness duration of ~10 years.

Subjects were checked for MRI contraindications and gave written informed consent to participate. The study was approved by the institutional review board of the medical faculty, Otto-von-Guericke-University, Magdeburg. Control subjects underwent routine clinical interview for history of neurological and psychiatric illnesses. Subjects with present or past neurological or psychiatric disorders or reported use of any drugs were excluded. Clinical and demographic details are summarized in Table 1. The control group comprised healthy subjects comparable in age, gender and handedness with the patients group (Table 1).

Diagnosis of paranoid schizophrenia following ICD-10 criteria was established by psychiatric evaluation using the psychopathological diagnosis system established by the Association for Methodology and Documentation in Psychiatry (Bobon and Ansseau, 1986). Furthermore, the structured clinical interview of the PANSS was applied to specifically assess schizophrenia-related symptomatology (Kay *et al*., 1987; Kay and Opler, 1987). The interview was performed directly after the MRI scan.

To corroborate the findings in this initial sample, a second, independent sample of patients and control subjects was assessed. Detailed population characteristics, methods and results are provided in the Supplementary material.

Magnetic resonance imaging acquisition and data analyses

Three-dimensional, T_1-weighted, high-resolution structural MRI scans of the brain were acquired on a 3 T Siemens MAGNETOM Trio scanner (Siemens) with an eight-channel phased-array head coil using a 3D-MPRAGE sequence (echo time = 4.77 ms, repetition time = 2500 ms, inversion time = 1100 ms, flip angle = 7°, bandwidth = 140 Hz/pixel, matrix = 256 × 256 × 192, isometric voxel size = 1.0 mm^3). Images were reoriented along the anterior commissure posterior commissure line, and the spatial coordinate origin was manually set to the anterior commissure (Frisoni *et al*., 2008).

Table 1 Mean demographic and clinical characteristics of the subjects including standard deviation (SD)

	Control subjects (n = 34, 14 females) Mean (SD)	Schizophrenia patients (n = 32, 11 females) Mean (SD)
Age	30.71 (7.10)	34.47 (8.63)
Chlorpromazine equivalent of daily antipsychotic dose (mg/d)		460.24 (389.35)
Duration of illness (years)		10.41 (8.73)
Female		13.18 (10.76)
Male		8.95 (7.34)
Age of onset (years)		25.03 (6.37)
Female		27.10 (7.98)
Male		23.95 (5.25)
PANSS total score		71.47 (21.61)
PANSS positive subscale score		16.75 (6.67)
PANSS negative subscale score		18.75 (8.72)
PANSS general psychopathology subscale score		36.03 (11.03)

Assessment of hippocampal volume

To perform a consecutive shape analysis of the left and right hippocampus, 66 T_1-weighted 3D-MPRAGEs were used for the manual hippocampus segmentation using the software package MRIcron (www.mricro.com). One rater (K.C.Z.) blind to group status made the volumetric assessment of the hippocampus for both hemispheres.

The hippocampus is symmetrically located in the medial temporal lobes and forms a bilaminar structure. The neuroanatomical criteria for hippocampal delineation were adapted from existing protocols (Jack *et al*., 1995; Pantel *et al*., 2000; Pruessner *et al*., 2000; Levitt *et al*., 2001; Narr *et al*., 2001, 2002) and based on the atlas of hippocampal anatomy (Duvernoy and Bourgouin, 1998; Duvernoy, 2005). For labelling, the coronal plane was used as default view. All voxels belonging to the hippocampus were labelled and stored as binary masks.

Reliability assessment of hippocampal volume

The same rater (K.C.Z.) repeatedly contoured the hippocampus from nine randomly chosen brains of both groups for intrarater reliability using intraclass correlation coefficients (ICC) for hippocampal volume ($ICC_{Intra} = 0.98$). A different investigator outlined the hippocampus of the same nine brains to establish inter-rater reliability ($ICC_{Inter} = 0.85$). In accordance with Portney and Watkins (2000), those ICCs reflect an almost perfect agreement.

Assessment of hippocampus shape

On the basis of the manually segmented hippocampal volumes of both hemispheres, the contours of the hippocampus masks were traced in coronal slices using the software MultiTracer (Woods, 2003) and stored as contour files in the ucf file format. This program allows the user to make use of anatomical landmarks by viewing images in all three orthogonal planes simultaneously (Thompson *et al*., 2004*a*, *b*). The hippocampus contours were used for shape analysis by the freely available shape tools software as JavaScripts developed at the laboratory of NeuroImaging (LONI, UCLA School of Medicine, Los Angeles) (Thompson *et al*., 1996*a*; Narr *et al*., 2004).

Briefly, the spatial coordinates of points on the hippocampal surface were unitized using the script InterpolateContour to a mesh of 100 × 150 surface points resulting to 15 000 describing vertices. Based on these uniform surface data for the right and left hippocampi of all subjects, a statistical analysis of shape differences between patients and control subjects was performed. The radial distance of each vertex to the hippocampus midline was calculated with the MedialDistance script (LONI, UCLA School of Medicine, Los Angeles) and stored. The average hippocampi, including all right or all left hippocampi, were computed using the ShapeAverage script and stored in the unc file format. The radial distances of each vertex to the hippocampus midline were transformed in greyscale analyse images for each individual hippocampus. Distance values between 0 and 10 mm correspond to grey values between 0 and 1000. The analyse images were stored as single slice data in a 100 × 150 matrix with the origin in the centre of each image (Fig. 1 and Table 2). The statistical analyses of these distance maps in terms of a full factorial analysis were accomplished by SPM5 described later in the text. To illustrate group differences in a 3D-format of the hippocampus, the SPM(t) maps of the full factorial analysis were added as a additional column to the ucf contour files of the average hippocampi. This was realized with the script ShapeAttribute (LONI, UCLA School of Medicine, Los Angeles). By using the script ShapeViewer (LONI, UCLA School of Medicine, Los Angeles), the SPM(t) maps were superposed on a mean hippocampus shape of all subjects for both hemispheres, respectively. T-values were colour coded in spectrum colours (maximum positive t-value as white, maximum negative t-value as black).

Assessment of hippocampus length

To assess the possibility that shape differences between groups arise from a longitudinal displacement of surface areas owing to differences in hippocampus length between groups, the hippocampus length of both hemispheres was assessed and compared between groups using a one-way ANOVA. The individual hippocampus length of every hemisphere was calculated using the script MedialDistance (LONI, UCLA School of Medicine, Los Angeles) by summation of the distances between the centres of all neighbouring hippocampal slices.

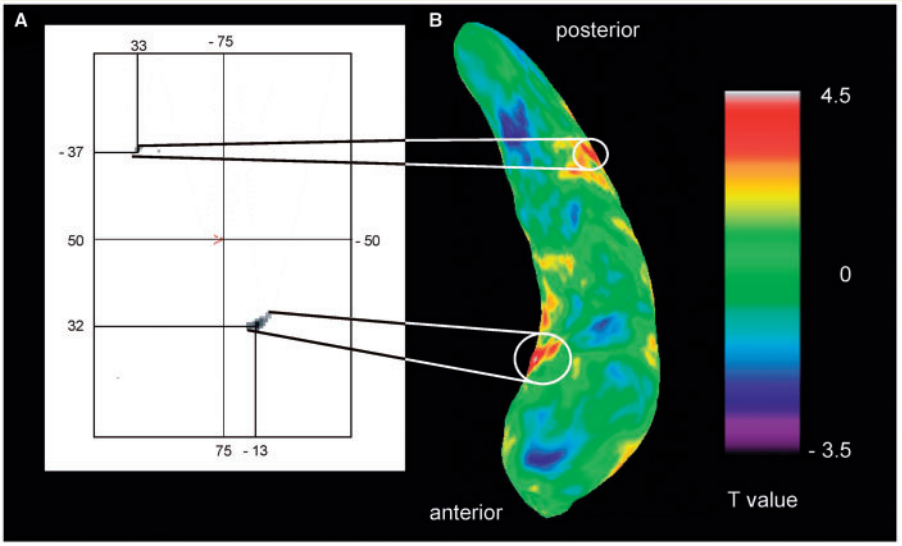

Figure 1 Control subjects > patients. (**A**) Map of SPM(*t*) values. (**B**) SPM(*t*) values superimposed on the left mean hippocampus shape of all subjects. Colour bar indicates FDR-corrected *t*-values (red reflects significant inward deformity in the patients with schizophrenia).

Table 2 SPM analysis of hippocampus shape between groups

Control subjects > patients	Side	K	Coordinates		*t*-value	*P*-value
			x	*y*		
CA1, anterior	Left	38	32	−13	4.49	0.045
CA1, posterior	Left	7	−37	33	4.42	0.045

$P_{FDR\text{-}corrected} < 0.05$.
K = number of voxels within clusters; *P*-value = statistical significance after correction for multiple comparisons (voxel level).

Surface-based identification of hippocampal subregions

Based on the anatomical magnetic resonance atlas of the hippocampus (Duvernoy and Bourgouin, 1998; Duvernoy, 2005) and magnetic resonance-based 3D models of the hippocampus formation generated by Frisoni *et al.* (2006, 2008), we mapped neuropathological hippocampal areas onto the averaged hippocampus.

Statistical analyses

Analyses of covariance

Population characteristics were compared by one-way ANOVAs. Group and side differences in hippocampus volume were assessed by ANCOVAs (factors: group and hemisphere) with age and whole brain volume as covariates. Owing to a one-by-one gender matching procedure, gender was not included as covariate in the ANCOVA. The significance level was set to 0.05. All statistical analyses were conducted with SPSS, v15.0.

Group differences in the hippocampus shape were initially explored in SPM5 applying a full factorial model with age and total intracranial volume as covariates. Directional *t*-contrasts were defined between groups. The corresponding SPM(*t*) values were thresholded at a level of significance of $P < 0.05$ (corrected). Any clusters showing significant findings were reported if surviving false discovery rate (FDR) correction for multiple comparisons at the $P < 0.05$ level (corrected).

Regression and correlation analyses

In the patient group, we additionally conducted linear regression and correlation analyses (Pearson correlation coefficients for metric data, Spearman Rho correlation coefficients for ordinal data, partial correlation coefficients with chlorpromazine-equivalent or PANSS positive subscale score as covariates). For that analysis, we extracted the beta values from significant clusters in the hippocampus shape analysis using the MarsBar toolbox for SPM (Brett *et al.*, 2002). The beta values were then entered in a regression and a correlation analysis with hippocampus volume, PANSS score (including positive, negative and general psychopathology subscale, as well as hypothesis driven single items from the positive scale: delusions, hallucinations), and chlorpromazine equivalent of daily antipsychotic dose as variables. Again, the significance level was set to 0.05.

Furthermore, an approximation of cumulative antipsychotic dose was estimated for every patient by multiplicating the chlorpromazine equivalent of the actual daily antipsychotic dose with years of disease duration. To assess whether the approximated cumulative antipsychotic dose was related to hippocampal volume loss and hippocampal shape alteration, a correlation analysis (Pearson correlation coefficient for metric data) was performed.

Results

Hippocampus shape analysis

The component of the full-factorial model comparing the schizophrenia group with the control subjects revealed a significant group effect. Group differences of shape in terms of an inward deformity were evident in the left, but not the right anterior and posterior hippocampus of patients with schizophrenia (Table 2, Fig. 1). These neuropathological changes were located in a hippocampal region that is known to consist of the CA1 subfield (Figs. 2 and 3). Concomitantly, the volume of the left hippocampus was also significantly reduced in the patients with schizophrenia (Fig. 4, Table 4). Owing to close matching, gender effects were not detected (male > female: $P_{FDR\text{-}corrected} > 1.000$; female > male: $P_{FDR\text{-}corrected} > 0.484$). We additionally found a significant positive correlation between shape deformity in the left posterior CA1 subfield and the hippocampus volume of the left hemisphere (Table 3).

Association between CA1 shape deformity and positive symptoms

For positive symptoms, the total subscale of the PANSS positive scale as well as the single items 'delusions' and 'hallucinations' were found to differentially correlate with the posterior CA1 subfield. Specifically, the hippocampal surface deformity in a region that consists of the CA1 subfield was negatively associated with the severity of positive symptoms (Table 3, scatter plot in Fig. 5). By controlling for the amount of daily antipsychotic treatment (partial correlation), that correlation remained significant ($r = -0.386$, $P = 0.035$). No significant association was found with the total score of the PANSS negative symptom scale and CA1 deformity.

Association between CA1 shape deformity and the prescribed antipsychotic treatment

Within the same regression model, anterior and posterior CA1 deformity was negatively associated with the amount of daily antipsychotic treatment in the patients with schizophrenia. Again, controlled for severity of positive symptoms (partial correlation), that association was significant too (CA1, anterior: $r = -0.428$,

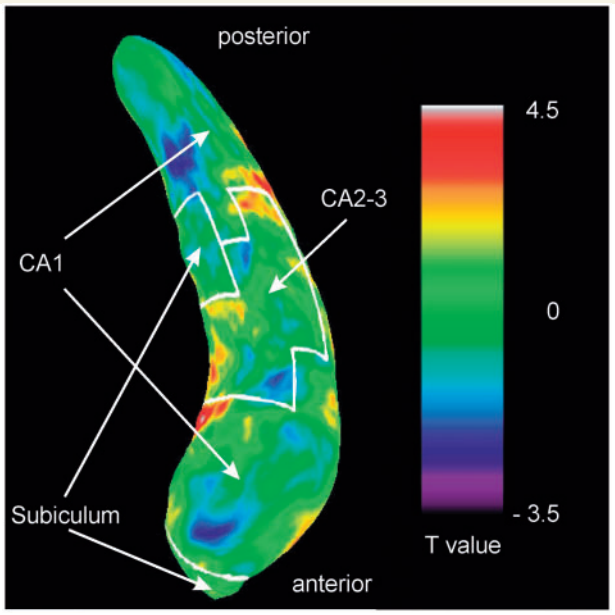

Figure 3 Allocation of the significant SPM clusters (Fig. 1) to the corresponding hippocampal surface subfields (Duvernoy and Bourgouin, 1998; Frisoni *et al*., 2006, 2008).

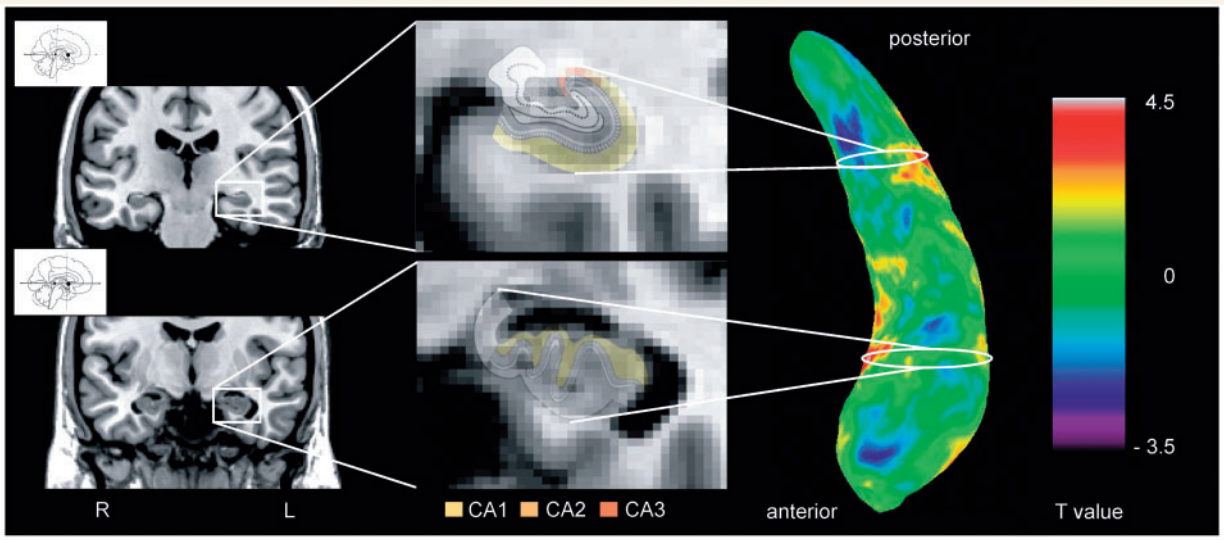

Figure 2 Coronal section of anterior (*bottom*) and posterior (*top*) hippocampus region. *Left*: Enlarged magnetic resonance detail of the left anterior and posterior hippocampus (www.mricron.com). *Middle*: Overlay of magnetic resonance and anatomical location of CA1-3 (Duvernoy, 2005). *Right*: Hippocampus shape (left hemisphere).

$P = 0.018$; CA1, posterior: $r = -0.399$, $P = 0.029$). Additionally, the lower left hippocampal volume was linked to a higher antipsychotic dosage (Table 3, scatter plots in Fig. 6).

Reduced hippocampal volume

Accompanying the hippocampal shape deformities in the left CA1 subfield, patients with schizophrenia showed significant hippocampal volume reductions in the left (main effect group) [$F(1,62) = 5.659$; $P = 0.020$] but not the right [$F(1,62) = 2.792$; $P = 0.100$] hemisphere (Table 4 and Fig. 4). There was no significant main effect regarding hemisphere and no significant interaction effect (group by hemisphere).

Estimated cumulative antipsychotic dose

In the patients with schizophrenia, the approximated cumulative antipsychotic dose did not correlate with hippocampal volume on either side (left: $r = -0.08$, $P = 0.658$; right: $r = -0.201$; $P = 0.263$). Furthermore, a correlation with the hippocampal surface inward deformation in the patients with schizophrenia was neither evident in the anterior ($r = 0.101$; $P = 0.590$) nor posterior CA1 subfield ($r = -0.309$, $P = 0.091$).

Hippocampus length

There were no significant group differences of hippocampus length between patients with schizophrenia and healthy control subjects [right: $F(1,64) = 0.177$, $P = 0.676$; left: $F(1,64) = 2.554$, $P = 0.115$].

Replication study

The main findings of this study were reproduced in a second, independent sample. Most importantly, the specific left hippocampal inward deformity attributable to CA1 in patients with schizophrenia was replicated. Moreover, the association of left

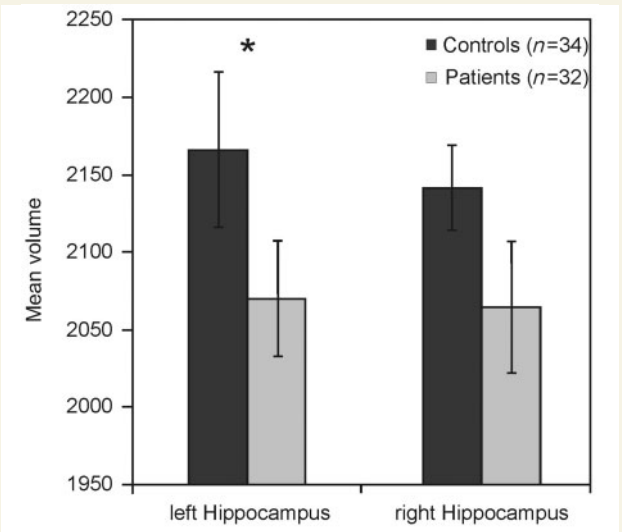

Figure 4 Mean left and right hippocampal volume (mm^3) of patients with schizophrenia and healthy control subjects. *ANCOVA $P < 0.05$.

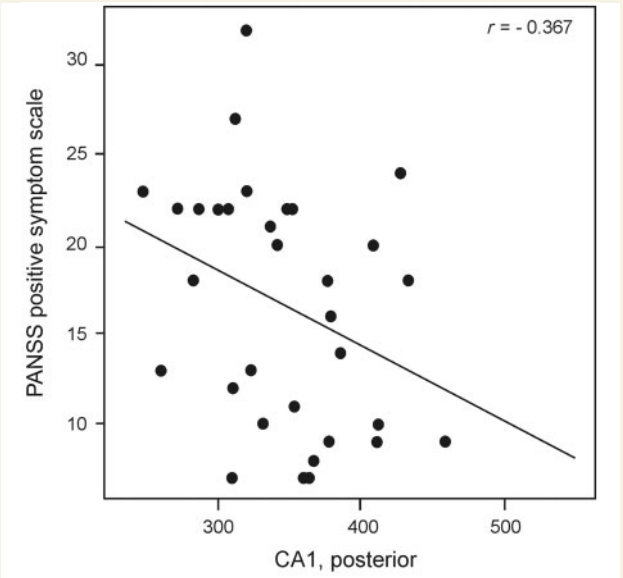

Figure 5 Scatter plot of the correlation (spearman rho) between the total score of the PANSS positive symptom scale and CA1 subfield inward deformity of the left hippocampus in patients with schizophrenia.

Table 3 Patient group linear regression and correlation analysis of hippocampus volume and shape deformity

	Side	Regression			Correlation	
		β	R^2	*P*-value	*r*	*P*-value
CA1, posterior—hippocampus volume	Left				0.381	0.031
CA1, posterior—positive symptomatology	Left				−0.367	0.039
CA1, posterior—hallucinatory behaviour	Left	−0.385	0.148	0.030	−0.392	0.027
CA1, posterior—delusions	Left	−0.361	0.130	0.042	−0.408	0.020
CA1, posterior—daily antipsychotic dose	Left	−0.374	0.140	0.038		
CA1, anterior—daily antipsychotic dose	Left	−0.401	0.161	0.025		
Hippocampus volume—daily antipsychotic dose	Left				−0.345	0.049

β = regression coefficient; R^2 = proportion of the variance explained by the linear regression model; *r* = correlation coefficient.

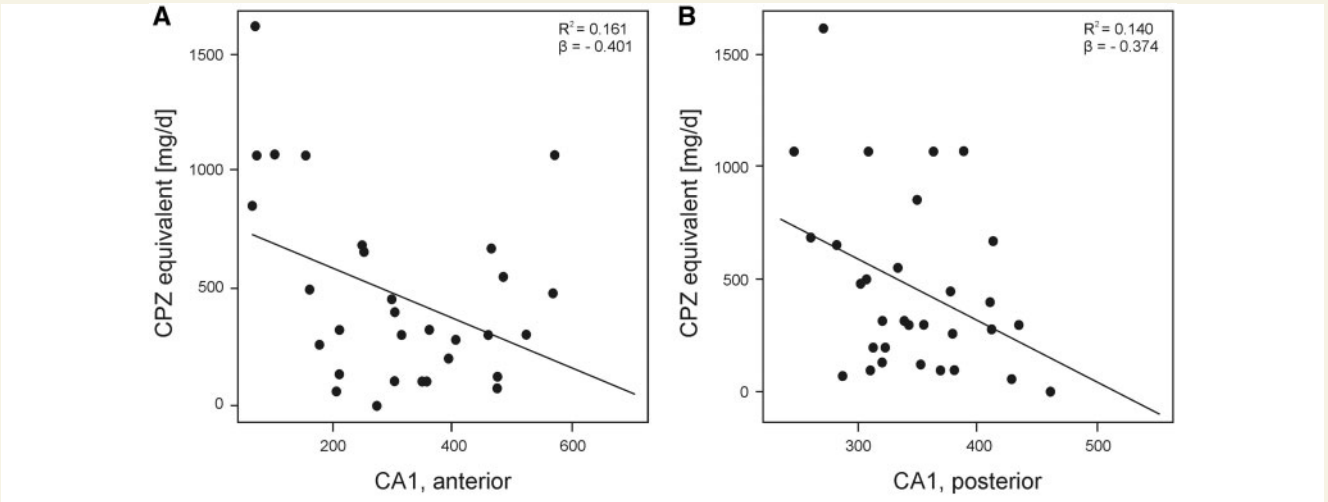

Figure 6 Scatter plot of the linear regression between the daily neuroleptic dose and the hippocampal CA1 subfield inward deformity of the left hippocampus (**A**: anterior, **B**: posterior) in the patients with schizophrenia. CPZ = chlorpromazine.

Table 4 Mean and standard error of the mean (sem) of hippocampus volume [mm^3] for the right (r) and left (l) hemisphere of schizophrenia patients and healthy controls. *ANCOVA $F_{1,62} = 5.659$; $p = 0.020$

		Control subjects (n = 34, 14 female)		Schizophrenia patients (n = 32, 11 female)	
Volume	Side	mean	sem	mean	sem
Hippocampus	l	2165.71*	49.13	2069.94	37.32
Hippocampus	r	2141.06	52.87	2064.53	42.60

Note: l = left; r = right.

hippocampal CA1 shrinkage with more pronounced positive symptoms was also evident in this sample. Finally, the link of CA1 shrinkage in patients with schizophrenia to the actually prescribed antipsychotic dosage was corroborated in the replication study. These results are provided in detail in the Supplementary material.

Discussion

Schizophrenic patients showed an inward deformity of the left anterior and posterior CA1 subfield along with a left hippocampal volume reduction. These abnormalities in the left hippocampus are closely associated with the severity of positive symptoms and specifically of delusions and hallucinations. Thus, the smaller CA1, the more prominent are delusions and hallucinations in the patients.

CA1 and total hippocampal volume are also associated with the amount of prescribed antipsychotics. Smaller CA1 statistically predict higher dosage of daily antipsychotic treatment. Accordingly, low hippocampal volume is accompanied by a more intense neuropharmacological treatment.

To our knowledge, this is the first report to show that CA1 deformities statistically predict the severity of positive symptoms and the required antipsychotic dosage in patients with schizophrenia. Furthermore, these results have been replicated in a second, independent sample of 19 healthy control subjects and 13 patients with schizophrenia (Supplementary material).

Shape deformities in left anterior and posterior CA1

The pattern of hippocampal deformity in the present sample of patients with schizophrenia suggests a unilateral deformity of the anterior and posterior CA1 subfield of the left hippocampus. In chronically ill patients with schizophrenia, such a deformation pattern has not explicitly been attributed to the CA1 partition before, even though this observation is supported by a pattern of hippocampal deformity in first-episode schizophrenia that has been described by previous studies (Bilder *et al*., 1995; Csernansky *et al*., 1998; Narr *et al*., 2001, 2002, 2004; Szeszko *et al*., 2003).

Inspecting the location of the posterior cluster in Fig. 3, it is evident that it is located in the proximity of the border of CA1 and CA2/3 and might possibly be misattributed to CA1 due to hippocampus length differences between groups. Though, a surface misallocation of the observed shape differences that might arise from such a longitudinal displacement of hippocampal surface areas due to, for example, a shortening of the hippocampus in schizophrenia, appears unlikely as there was no significant group difference of hippocampus length detectable in either hemisphere.

Role of CA1 in schizophrenia

The functional importance of the hippocampal CA1 subfield arises from its specific neuronal connectivity. Major efferences from the CA1 project to the cortex (Van Hoesen and Hyman, 1990) while

neighbouring CA3 neurons interconnect with CA1 through the Shaffer collaterals.

Because hippocampal subregions are interconnected to form a circuit, a 'lesion' in one subregion might cause secondary dysfunction in other subregions. CA1 receives its main input via the Shaffer collaterals from CA3 and from the entorhinal cortex (Small *et al*., 2011). The loss of CA3 GABAergic interneurons in patients with schizophrenia may lead to an overstimulation of glutamatergic AMPA- (α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid) receptors. In conjunction with increased synaptic glutamate release, this—in turn—might cause hyperactivity in the CA1 subfield (Benes, 1999). Supporting evidence arises from several functional MRI studies that have reported a hyperactive state in CA1 in patients with schizophrenia (Kawasaki *et al*., 1992; Gur *et al*., 1995; Heckers *et al*., 1998). Furthermore, dopamine hyperfunction, which inhibits glutamatergic NMDA input, is shown to dramatically reduce direct cortical input to CA1. Thus, such a hyperglutamatergic state in the CA1 subfield, caused by a deficient inhibition of CA3 and a dopaminergic hyperfunction, might not only cause neuronal hyperactivity but also—because of the neurotoxicity of glutamate—neuronal damage resulting in volume loss in CA1. Such pathology affecting CA1, as evident in the present data, may lead to a functional disconnection of the hippocampus from its target areas. It thus provides support for the hypothesis that schizophrenia involves a disturbance of the connections between the hippocampus and other downstream brain regions (Weinberger *et al*., 1992), which might impair functionality of the latter.

CA1 inward deformities are closely related to positive symptoms

CA1 shrinkage was also found to be associated with measures of delusions and hallucinations. Our data show for the first time, that morphological deformities in CA1 statistically predict severity of hallucinations and delusions. Previous studies failed to find an association between hippocampal shape deformities and symptom severity in patients with schizophrenia (Csernansky *et al*., 1998, 2002). Csernansky *et al*. (1998, 2002) used general pattern matching and a template of hippocampal neuroanatomy to represent hippocampus shape using eigenvectors. With this technique, the eigenvectors obtained from each individual warp do not directly reflect stereotaxic information but rather provide an aggregate measure of general hippocampal shape differences between groups. Possibly, this approach is not suitable to detect correlations between subfield deformities and symptom severity that appear to be highly regionally specific.

To date, symptomatology in patients with schizophrenia was linked to CA1 alterations only on a functional level. Schobel *et al*. (2009) reported an association between a functional hyperactivation of CA1 and increased positive symptoms. This raises the intriguing possibility that hyperactivity in CA1 may—because of disturbed information processing for example—actually drive the psychotic symptoms of hallucinations and delusions; core symptoms of schizophrenia. This putatively crucial role of hippocampal hyperactivity is supported by the observation that schizophrenia-like psychotic symptoms in patients with temporal lobe epilepsy are associated with such hyperactive hippocampal states (Elliott *et al*., 2009*a*, *b*). Such hippocampal hyperactivity has been postulated by a number of PET (Friston *et al*., 1992) and functional MRI studies (Gur *et al*., 1995; Kawasaki *et al*., 1992; Medoff *et al*., 2001; Malaspina *et al*., 2004) observing increased cerebral blood flow in mediotemporal and hippocampal regions. Several studies applying memory tasks have observed decreased hippocampal activation in these tasks (Heckers *et al*., 1998, 1999; Ragland *et al*., 1998; Weiss and Heckers, 2001). But in fact, this finding from functional MRI and PET studies applying between-task comparisons does not directly contradict the concept of a basally increased neuronal activity of the hippocampus. If there is a basally increased hippocampal activity, it might well be that such a pre-existing activity only increases to a lesser degree in a hippocampus-dependent task compared with states with a lower basal hippocampus activity (Heckers *et al*., 1998; Weiss and Heckers, 2001).

In the study by Schobel *et al*. (2009), the hippocampal hyperactivity was specifically restricted to CA1, and not present in CA3 or dentate gyrus, underscoring the special importance of the hippocampal CA1 subfield in schizophrenia. This finding strikingly reflects computational and neurobiological models of the pathogenesis of psychosis that have highlighted the critical role of CA1 in the development of core psychotic symptoms in schizophrenia (Krieckhaus *et al*., 1992; Benes, 1999; Otmakhova and Lisman, 2000; Lisman and Otmakhova, 2001; Lisman *et al*., 2010; Zhang *et al*., 2012). This again relates to the finding of Schobel *et al*. (2009) that CA1 hyperactivity is specifically predictive of the development of full-blown psychosis in a subgroup of prodromal subjects and is specifically related to the total positive symptoms subscore of the PANSS and to delusions, both in schizophrenic and prodromal patients.

It is conceivable that the structural CA1 alteration observed in the present study is a consequence of a hyperactive state of the hippocampus CA1 subfield as described by Schobel *et al*. (2009). In this context, it fits well with the fact that CA1 inward deformity is directly correlated with positive symptoms, especially delusions and hallucinations in the present study.

Anterior and posterior CA1 deformities statistically predict psychopharmacological treatment

Deformities of CA1 are not only associated to symptomatology but also statistically predict the amount of antipsychotics applied to alleviate those symptoms. Our data show that the smaller the CA1, the higher the ordinated daily antipsychotic dose. The alternative explanation of this relation, i.e. a hippocampal volume reduction and shape alteration due to long-term effects of antipsychotic medication (for a detailed overview, see Moncrieff and Leo, 2010) appears unlikely, considering the finding that approximated cumulative antipsychotic dose is not related to volume and shape alterations in the present sample of patients with schizophrenia.

To date, only two studies have been published addressing the relationship between antipsychotic treatment and hippocampal volume, but not the exact location via shape analyses (Bogerts *et al*., 1993*b*; Pegues *et al*., 2003). Pegues *et al*. (2003) reported no significant correlations between hippocampal volumes and medication level. Bogerts *et al*. (1993*b*) similarly reported a non-significant correlation between temporolimbic tissue volumes with maximum doses of antipsychotic drug treatment. Our data show a significant correlation between hippocampal volume and psychopharmacological treatment contradicting both studies. These discrepancies might be the result of different methodologies applied. Bogerts *et al*. (1993*b*) used a 1.0 T magnetic resonance system with a whole head image resolution of $1.0 \times 0.6 \times 3.1$ mm. Pegues *et al*. (2003) performed all MRI studies with a 1.5 T Magnetom using a $1.0\,m \times 1.4 \times 3$ mm resolution. In the present study, we used a 3 T Magnetom with a much higher resolution of 1 mm^3 and a higher structural precision. Thus, the discrepancies between our results and the two mentioned studies (Bogerts, 1993*a*; Pegues *et al*., 2003) may arise from the lower image resolution and as consequence a reduced precision in the manual segmentation of small brain structures with irregular shapes, like the hippocampus.

No previous study has investigated the relationship between the deformation of a distinct hippocampal subregion and antipsychotic treatment in patients with schizophrenia. Thus, to our knowledge, this is the first demonstration of a direct causal relationship between morphological abnormalities and the necessary pharmacological treatment in schizophrenia. As CA1 is additionally predicting symptom severity, it appears that the smaller the CA1, the more severe the symptomatology and, hypothetically, the higher the antipsychotic dosage that is required to reduce symptomatology.

These clear-cut findings notwithstanding, it appears necessary to point out that other important aspects such as genetic, social and psychological factors, the assessment of whose influence is beyond the scope of this study, also play a crucial role in determining the individual dosage of antipsychotic medication.

Reduced left hippocampal volume

The schizophrenic patients in our study showed reduced left hippocampal volume. This finding is consistent with several recent studies that have documented larger right, compared with left hippocampal volumes in both schizophrenic patients and control subjects (Pearlson *et al*., 1997; Marsh *et al*., 1999; Velakoulis *et al*., 1999; Niemann *et al*., 2000; Wang *et al*., 2001).

Accordingly, previous studies provide further evidence that limbic structure volumes are more prominently reduced in the left hemisphere and additionally show that a left hemispheric volume reduction was evident in patients with first-episode schizophrenia, whereas in chronically ill patients, the hippocampi of both hemispheres are affected. A probable explanation for these different laterality findings in the two patient samples is that pre-existing bilateral hippocampal pathology occurs in more severe forms of the illness and predisposes to poorer treatment response and a worse outcome.

Our data indeed show significant volume reduction of left hippocampus even though our sample mainly consisted of chronically ill patients with schizophrenia. An explanation based on the argumentation of Bogerts *et al*. (1993*b*) could be that our patient sample consisted of patients with a less severe course of the disease and thus only a lateralized volume reduction of the hippocampus, promising better treatment response and outcome. Clearly, only longitudinal studies may establish with certainty whether grey matter volume is lost or simply never fully developed.

Limitations

Nevertheless, some caveats regarding the interpretation of our findings should be highlighted. First, the use of hippocampal surface models relies on manual tracing, and systematic bias owing to changes in the anatomy of the hippocampus of patients might adversely affect its reliability. The reliability of the method has been shown to be high (Thompson *et al*., 2004*a*); however, it is possible that there is a systematic bias in these tracings that is correlated with diagnosis. Although the tracings are made by raters blind to diagnosis, any difference in image contrast between patients with schizophrenia and healthy subjects could also alter the boundaries. Finally, the localization of neuroanatomical regions of the hippocampal formation is far from perfect owing to inter-individual variations of neuroanatomy and variability of image quality and resolution.

A further shortcoming may be the fact that none of the patients were drug-naïve at the time of study. However, all patients had received second generation antipsychotics, and the non-significant correlation between illness duration and hippocampal volume ($r = 0.235$; $P = 0.211$) argues against a strong influence of antipsychotic medication on the dependent variables. This is also consistent with the majority of hippocampal voluming studies in patients with schizophrenia (Bogerts *et al*., 1993*b*; Kawasaki *et al*., 1993; Marsh *et al*., 1994; Zipursky *et al*., 1994; Csernansky *et al*., 1998; Whitworth *et al*., 1998; Stefanis *et al*., 1999; Altshuler *et al*., 2000; Gur *et al*., 2000).

Conclusion

This is the first evidence of a link between the severity of positive symptoms in patients with schizophrenia and a morphological alteration of a distinct hippocampal subregion, namely CA1. This deformation might be the consequence of a disease-specific hyperactive hippocampal state presumably leading to atrophic changes, possibly reflecting neuronal or glial loss in the course of the disease. As deficits in CA1 may further cause deficits in connected processing circuits, this abnormality might be critical for the development of schizophrenia and its symptomatology. Furthermore, CA1 shrinkage is statistically related to the dosage of antipsychotic maintenance treatment. Thus, CA1 apparently plays an important role in the pathophysiology of schizophrenia and might represent a biological marker of the clinical severity in this disease.

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Supplementary material

Supplementary material is available at *Brain* online.

References

Altshuler LL, Bartzokis G, Grieder T, Curran J, Jimenez T, Leight K, et al. An MRI study of temporal lobe structures in men with bipolar disorder or schizophrenia. Biol Psychiatry 2000; 48: 147–62.

Benes FM. Evidence for altered trisynaptic circuitry in schizophrenic hippocampus. Biol Psychiatry 1999; 46: 589–99.

Bilder RM, Bogerts B, Ashtari M, Wu H, Alvir JM, Jody D, et al. Anterior hippocampal volume reductions predict frontal lobe dysfunction in first episode schizophrenia. Schizophr Res 1995; 17: 47–58.

Bobon D, Ansseau M. The AMDP-system in clinical psychopharmacology. Pharmacopsychiatry 1986; 19: 55–7.

Bogerts B. Neuropathology of schizophrenias. Fortschr Neurol Psychiatr 1984; 52: 428–37.

Bogerts B. Schizophrenien als Erkrankungen des limbischen Systems. In: Huber G, editor. Basisstadien endogener Psychosen und das Borderline-Problem. Stuttgart: Schattauer; 1985.

Bogerts B. Recent advances in the neuropathology of schizophrenia. Schizophr Bull 1993a; 19: 431–45.

Bogerts B, Lieberman JA, Ashtari M, Bilder RM, Degreef G, Lerner G, et al. Hippocampus-amygdala volumes and psychopathology in chronic schizophrenia. Biol Psychiatry 1993b; 33: 236–46.

Breier A, Buchanan RW, Elkashef A, Munson RC, Kirkpatrick B, Gellad F. Brain morphology and schizophrenia. A magnetic resonance imaging study of limbic, prefrontal cortex, and caudate structures. Arch Gen Psychiatry 1992; 49: 921–6.

Brett M, Anton JL, Valabregue R, Poline JB. Region of interest analysis using an SPM toolbox. In: 8th International Conference on Functional Mapping of the Human Brain, Sendai, Japan; 2002.

Csernansky JG, Joshi S, Wang L, Haller JW, Gado M, Miller JP, et al. Hippocampal morphometry in schizophrenia by high dimensional brain mapping. Proc Natl Acad Sci USA 1998; 95: 11406–11.

Csernansky JG, Wang L, Jones D, Rastogi-Cruz D, Posener JA, Heydebrand G, et al. Hippocampal deformities in schizophrenia characterized by high dimensional brain mapping. Am J Psychiatry 2002; 159: 2000–6.

DeLisi LE, Dauphinais ID, Gershon ES. Perinatal complications and reduced size of brain limbic structures in familial schizophrenia. Schizophr Bull 1988; 14: 185–91.

Duvernoy H, Bourgouin P. The human hippocampus: functional anatomy, vascularization and serial sections with MRI; with 47 tables. Berlin: Springer; 1998.

Duvernoy HM. The human hippocampus: functional anatomy, vascularization and serial sections with MRI. Berlin, Heidelberg. New York: Springer; 2005.

Elliott B, Joyce E, Shorvon S. Delusions, illusions and hallucinations in epilepsy: 1. Elementary phenomena. Epilepsy Res 2009a; 85: 162–71.

Elliott B, Joyce E, Shorvon S. Delusions, illusions and hallucinations in epilepsy: 2. Complex phenomena and psychosis. Epilepsy Res 2009b; 85: 172–86.

Frisoni GB, Sabattoli F, Lee AD, Dutton RA, Toga AW, Thompson PM. In vivo neuropathology of the hippocampal formation in AD: a radial mapping MR-based study. Neuroimage 2006; 32: 104–10.

Frisoni GB, Ganzola R, Canu E, Rub U, Pizzini FB, Alessandrini F, et al. Mapping local hippocampal changes in Alzheimer's disease and normal ageing with MRI at 3 Tesla. Brain 2008; 131: 3266–76.

Friston KJ, Liddle PF, Frith CD, Hirsch SR, Frackowiak RS. The left medial temporal region and schizophrenia. A PET study. Brain 1992; 115 (Pt 2): 367–82.

Gur RE, Mozley PD, Resnick SM, Mozley LH, Shtasel DL, Gallacher F, et al. Resting cerebral glucose metabolism in first-episode and previously treated patients with schizophrenia relates to clinical features. Arch Gen Psychiatry 1995; 52: 657–67.

Gur RE, Turetsky BI, Cowell PE, Finkelman C, Maany V, Grossman RI, et al. Temporolimbic volume reductions in schizophrenia. Arch Gen Psychiatry 2000; 57: 769–75.

Haller JW, Christensen GE, Joshi SC, Newcomer JW, Miller MI, Csernansky JG, et al. Hippocampal MR imaging morphometry by means of general pattern matching. Radiology 1996; 199: 787–91.

Harrison PJ, Eastwood SL. Neuropathological studies of synaptic connectivity in the hippocampul formation in schizophrenia. Hippocampus 2001; 11: 508–519.

Heckers S. Neuropathology of schizophrenia: cortex, thalamus, basal ganglia, and neurotransmitter-specific projection systems. Schizophr Bull 1997; 23: 403–21.

Heckers S, Rauch SL, Goff D, Savage CR, Schacter DL, Fischman AJ, et al. Impaired recruitment of the hippocampus during conscious recollection in schizophrenia. Nat Neurosci 1998; 1: 318–23.

Heckers S, Goff D, Schacter DL, Savage CR, Fischman AJ, Alpert NM, et al. Functional imaging of memory retrieval in deficit vs nondeficit schizophrenia. Arch Gen Psychiatry 1999; 56: 1117–23.

Jack CR Jr, Theodore WH, Cook M, McCarthy G. MRI-based hippocampal volumetrics: data acquisition, normal ranges, and optimal protocol. Magn Reson Imaging 1995; 13: 1057–64.

Kawasaki Y, Suzuki M, Maeda Y, Urata K, Yamaguchi N, Matsuda H, et al. Regional cerebral blood flow in patients with schizophrenia. A preliminary report. Eur Arch Psychiatry Clin Neurosci 1992; 241: 195–200.

Kawasaki Y, Maeda Y, Urata K, Higashima M, Yamaguchi N, Suzuki M, et al. A quantitative magnetic resonance imaging study of patients with schizophrenia. Eur Arch Psychiatry Clin Neurosci 1993; 242: 268–72.

Kay SR, Opler LA. The positive-negative dimension in schizophrenia: its validity and significance. Psychiatr Dev 1987; 5: 79–103.

Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr Bull 1987; 13: 261–76.

Krieckhaus EE, Donahoe JW, Morgan MA. Paranoid schizophrenia may be caused by dopamine hyperactivity of CA1 hippocampus. Biol Psychiatry 1992; 31: 560–70.

Levitt JG, Blanton RE, Caplan R, Asarnow R, Guthrie D, Toga AW, et al. Medial temporal lobe in childhood-onset schizophrenia. Psychiatry Res 2001; 108: 17–27.

Lisman JE, Otmakhova NA. Storage, recall, and novelty detection of sequences by the hippocampus: elaborating on the SOCRATIC model to account for normal and aberrant effects of dopamine. Hippocampus 2001; 11: 551–68.

Lisman JE, Pi HJ, Zhang Y, Otmakhova NA. A thalamo-hippocampal-ventral tegmental area loop may produce the positive feedback that underlies the psychotic break in schizophrenia. Biol Psychiatry 2010; 68: 17–24.

Malaspina D, Harkavy-Friedman J, Corcoran C, Mujica-Parodi L, Printz D, Gorman JM, et al. Resting neural activity distinguishes subgroups of schizophrenia patients. Biol Psychiatry 2004; 56: 931–7.

Marsh L, Suddath RL, Higgins N, Weinberger DR. Medial temporal lobe structures in schizophrenia: relationship of size to duration of illness. Schizophr Res 1994; 11: 225–38.

Marsh L, Lim KO, Hoff AL, Harris D, Beal M, Minn K, et al. Severity of schizophrenia and magnetic resonance imaging abnormalities: a comparison of state and veterans hospital patients. Biol Psychiatry 1999; 45: 49–61.

Medoff DR, Holcomb HH, Lahti AC, Tamminga CA. Probing the human hippocampus using rCBF: contrasts in schizophrenia. Hippocampus 2001; 11: 543–50.

Moncrieff J, Leo J. A systematic review of the effects of antipsychotic drugs on brain volume. Psychol Med 2010; 40: 1409–22.

Narr KL, Thompson PM, Sharma T, Moussai J, Blanton R, Anvar B, et al. Three-dimensional mapping of temporo-limbic regions and the lateral ventricles in schizophrenia: gender effects. Biol Psychiatry 2001; 50: 84–97.

Narr KL, van Erp TG, Cannon TD, Woods RP, Thompson PM, Jang S, et al. A twin study of genetic contributions to hippocampal morphology in schizophrenia. Neurobiol Dis 2002; 11: 83–95.

Narr KL, Thompson PM, Szeszko P, Robinson D, Jang S, Woods RP, et al. Regional specificity of hippocampal volume reductions in first-episode schizophrenia. Neuroimage 2004; 21: 1563–75.

Niemann K, Hammers A, Coenen VA, Thron A, Klosterkotter J. Evidence of a smaller left hippocampus and left temporal horn in both patients with first episode schizophrenia and normal control subjects. Psychiatry Res 2000; 99: 93–110.

Otmakhova NA, Lisman JE. Dopamine, serotonin, and noradrenaline strongly inhibit the direct perforant path-CA1 synaptic input, but have little effect on the Schaffer collateral input. Ann N Y Acad Sci 2000; 911: 462–4.

Pantel J, O'Leary DS, Cretsinger K, Bockholt HJ, Keefe H, Magnotta VA, et al. A new method for the in vivo volumetric measurement of the human hippocampus with high neuroanatomical accuracy. Hippocampus 2000; 10: 752–8.

Pearlson GD, Barta PE, Powers RE, Menon RR, Richards SS, Aylward EH, et al. Ziskind-Somerfeld Research Award 1996. Medial and superior temporal gyral volumes and cerebral asymmetry in schizophrenia versus bipolar disorder. Biol Psychiatry 1997; 41: 1–14.

Pegues MP, Rogers LJ, Amend D, Vinogradov S, Deicken RF. Anterior hippocampal volume reduction in male patients with schizophrenia. Schizophr Res 2003; 60: 105–15.

Portney LG, Watkins MP. Foundations of clinical research: applications to practice. Upper Saddle River, NJ: Prentice Hall; 2000.

Pruessner JC, Li LM, Serles W, Pruessner M, Collins DL, Kabani N, et al. Volumetry of hippocampus and amygdala with high-resolution MRI and three-dimensional analysis software: minimizing the discrepancies between laboratories. Cereb Cortex 2000; 10: 433–42.

Ragland JD, Gur RC, Glahn DC, Censits DM, Smith RJ, Lazarev MG, et al. Frontotemporal cerebral blood flow change during executive and declarative memory tasks in schizophrenia: a positron emission tomography study. Neuropsychology 1998; 12: 399–413.

Schobel SA, Lewandowski NM, Corcoran CM, Moore H, Brown T, Malaspina D, et al. Differential targeting of the CA1 subfield of the hippocampal formation by schizophrenia and related psychotic disorders. Arch Gen Psychiatry 2009; 66: 938–46.

Shenton ME, Gerig G, McCarley RW, Szekely G, Kikinis R. Amygdala-hippocampal shape differences in schizophrenia: the application of 3D shape models to volumetric MR data. Psychiatry Res 2002; 115: 15–35.

Small SA, Schobel SA, Buxton RB, Witter MP, Barnes CA. A pathophysiological framework of hippocampal dysfunction in ageing and disease. Nat Rev Neurosci 2011; 12: 585–601.

Stefanis N, Frangou S, Yakeley J, Sharma T, O'Connell P, Morgan K, et al. Hippocampal volume reduction in schizophrenia: effects of genetic risk and pregnancy and birth complications. Biol Psychiatry 1999; 46: 697–702.

Suddath RL, Casanova MF, Goldberg TE, Daniel DG, Kelsoe JR Jr, Weinberger DR. Temporal lobe pathology in schizophrenia: a quantitative magnetic resonance imaging study. Am J Psychiatry 1989; 146: 464–72.

Szeszko PR, Goldberg E, Gunduz-Bruce H, Ashtari M, Robinson D, Malhotra AK, et al. Smaller anterior hippocampal formation volume in antipsychotic-naive patients with first-episode schizophrenia. Am J Psychiatry 2003; 160: 2190–7.

Thompson PM, Schwartz C, Toga AW. High-resolution random mesh algorithms for creating a probabilistic 3D surface atlas of the human brain. Neuroimage 1996a; 3: 19–34.

Thompson PM, Schwartz C, Lin RT, Khan AA, Toga AW. Three-dimensional statistical analysis of sulcal variability in the human brain. J Neurosci 1996b; 16: 4261–74.

Thompson PM, MacDonald D, Mega MS, Holmes CJ, Evans AC, Toga AW. Detection and mapping of abnormal brain structure with a probabilistic atlas of cortical surfaces. J Comput Assist Tomogr 1997; 21: 567–81.

Thompson PM, Hayashi KM, De Zubicaray GI, Janke AL, Rose SE, Semple J, et al. Mapping hippocampal and ventricular change in Alzheimer disease. Neuroimage 2004a; 22: 1754–66.

Thompson PM, Hayashi KM, Sowell ER, Gogtay N, Giedd JN, Rapoport JL, et al. Mapping cortical change in Alzheimer's disease, brain development, and schizophrenia. Neuroimage 2004b; 23 (Suppl 1): S2–18.

Van Hoesen GW, Hyman BT. Hippocampal formation: anatomy and the patterns of pathology in Alzheimer's disease. Prog Brain Res 1990; 83: 445–57.

Velakoulis D, Pantelis C, McGorry PD, Dudgeon P, Brewer W, Cook M, et al. Hippocampal volume in first-episode psychoses and chronic schizophrenia: a high-resolution magnetic resonance imaging study. Arch Gen Psychiatry 1999; 56: 133–41.

Wang L, Joshi SC, Miller MI, Csernansky JG. Statistical analysis of hippocampal asymmetry in schizophrenia. Neuroimage 2001; 14: 531–45.

Weinberger DR, Berman KF, Suddath R, Torrey EF. Evidence of dysfunction of a prefrontal-limbic network in schizophrenia: a magnetic resonance imaging and regional cerebral blood flow study of discordant monozygotic twins. Am J Psychiatry 1992; 149: 890–7.

Weiss AP, Heckers S. Neuroimaging of declarative memory in schizophrenia. Scand J Psychol 2001; 42: 239–50.

Whitworth AB, Honeder M, Kremser C, Kemmler G, Felber S, Hausmann A, et al. Hippocampal volume reduction in male schizophrenic patients. Schizophr Res 1998; 31: 73–81.

Woods RP. Multitracer: a Java-based tool for anatomic delineation of grayscale volumetric images. Neuroimage 2003; 19: 1829–34.

Zhang Y, Yoshida T, Katz DB, Lisman JE. NMDAR antagonist action in thalamus imposes delta oscillations on the hippocampus. J Neurophysiol 2012; 107: 3181–9.

Zierhut K, Bogerts B, Schott B, Fenker D, Walter M, Albrecht D, et al. The role of hippocampus dysfunction in deficient memory encoding and positive symptoms in schizophrenia. Psychiatry Res 2010; 183: 187–94.

Zipursky RB, Marsh L, Lim KO, DeMent S, Shear PK, Sullivan EV, et al. Volumetric MRI assessment of temporal lobe structures in schizophrenia. Biol Psychiatry 1994; 35: 501–16.

Zola-Morgan S, Squire LR, Amaral DG. Human amnesia and the medial temporal region: enduring memory impairment following a bilateral lesion limited to field CA1 of the hippocampus. J Neurosci 1986; 6: 2950–67.