Hippocampal and caudate volume reductions in antipsychotic-naive first-episode schizophrenia

Bjørn H. Ebdrup, MD, PhD; Birte Glenthøj, MD, DMSc; Hans Rasmussen, PhD; Bodil Aggernaes, MD, PhD; Annika R. Langkilde, MD, PhD; Olaf B. Paulson, MD, DMSc; Henrik Lublin, MD, DMSc; Arnold Skimminge, MSc; William Baaré, PhD

Ebdrup, Glenthøj, Rasmussen, Aggernaes, Lublin — Center for Neuropsychiatric Schizophrenia Research and Center for Clinical Intervention and Neuropsychiatric Schizophrenia Research, Psychiatric Center Glostrup, Copenhagen University Hospital, Glostrup; Ebdrup, Langkilde, Paulson, Skimminge, Baaré — Danish Research Centre for Magnetic Resonance, MR-Department, Copenhagen University Hospital Hvidovre, Hvidovre; Paulson, Baaré — Center for Integrated Molecular Brain Imaging and Neurobiology Research Unit, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark

Background: Enlarged ventricles and reduced hippocampal volume are consistently found in patients with first-episode schizophrenia. Studies investigating brain structure in antipsychotic-naive patients have generally focused on the striatum. In this study, we examined whether ventricular enlargement and hippocampal and caudate volume reductions are morphological traits of antipsychotic-naive first-episode schizophrenia. **Methods:** We obtained high-resolution 3-dimensional T_1-weighted magnetic resonance imaging scans for 38 antipsychotic-naive first-episode schizophrenia patients and 43 matched healthy controls by use of a 3-T scanner. We warped the brain images to each other by use of a high-dimensional intersubject registration algorithm. We performed voxel-wise group comparisons with permutation tests. We performed small volume correction for the hippocampus, caudate and ventricles by use of a false discovery rate correction ($p < 0.05$) to control for multiple comparisons. We derived and analyzed estimates of brain structure volumes. We grouped patients as those with ($n = 9$) or without ($n = 29$) any lifetime substance abuse to examine the possible effects of substance abuse. **Results:** We found that hippocampal and caudate volumes were decreased in patients with first-episode schizophrenia. We found no ventricular enlargement, differences in global volume or significant associations between tissue volume and duration of untreated illness or psychopathology. The hippocampal volume reductions appeared to be influenced by a history of substance abuse. Exploratory analyses indicated reduced volume of the nucleus accumbens in patients with first-episode schizophrenia. **Limitations:** This study was not a priori designed to test for differences between schizophrenia patients with or without lifetime substance abuse, and this subgroup was small. **Conclusion:** Reductions in hippocampal and caudate volume may constitute morphological traits in antipsychotic-naive first-episode schizophrenia patients. However, the clinical implications of these findings are unclear. Moreover, past substance abuse may accentuate hippocampal volume reduction. Magnetic resonance imaging studies addressing the potential effects of substance abuse in antipsychotic-naive first-episode schizophrenia patients are warranted.

Introduction

Magnetic resonance imaging (MRI) studies have demonstrated the presence of structural brain abnormalities in multiple brain regions in chronic schizophrenia patients compared with healthy controls.[1] Although, volume changes have also been observed in various brain regions in first-episode schizophrenia patients,[2] only hippocampal volume reduction and ventricular enlargement are consistently present, as shown in 2 recent meta-analyses.[3,4] Inconsistencies among studies are probably because of differences in methods, samples sizes and sample composition (e.g., studies vary

Correspondence to: Dr. B.H. Ebdrup, Center for Neuropsychiatric Schizophrenia Research, Center for Clinical Intervention and Neuropsychiatric Schizophrenia Research, Psychiatric Center Glostrup, University Hospital Glostrup, DK-2600 Glostrup, Denmark; fax 45 4323 4653; bebdrup@cnsr.dk

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in the inclusion criteria regarding previous exposure to antipsychotic medications and substance abuse or dependence).

Numerous studies point toward hippocampal involvement in schizophrenia (for reviews see[5,6]). Volumetric reductions in hippocampus, however, are not pathognomonic for schizophrenia, but they have been associated with numerous neuropsychiatric disorders, including substance abuse.[7] Moreover, typical and atypical antipsychotics may affect hippocampal volumes differently.[8] In antipsychotic-naive patients, significant hippocampal reductions have been reported,[9] although not consistently.[10] The clinical implications of hippocampal involvement in antipsychotic-naive schizophrenia patients are unclear. However, hippocampal reductions may be associated with illness duration and psychopathology.[11]

Ventricular enlargement is also not specific for schizophrenia.[12] Nevertheless, recent studies suggest that ventricular enlargement may progress during the course of the disease and may be related to outcome[13] or antipsychotic treatment.[14]

Studies investigating minimally medicated and antipsychotic-naive schizophrenia patients have often focused on the striatum, which consists of the caudate nucleus, putamen and nucleus accumbens.[15] Striatal volume reductions are not consistently found in medicated first-episode patients, likely because antipsychotic treatment in itself can induce alterations in the striatum (for review see[16]). Nevertheless, a recent meta-analysis of voxel-based structural MRI studies in first-episode patients found the presence of caudate nucleus reductions as compared with chronic schizophrenia patients.[2] Moreover, nonpsychotic children of psychotic individuals have been shown to have smaller caudate nuclei.[17] Absolute volume reductions in the putamen and nucleus accumbens[15,18,19] have also been observed, although significant changes have only been observed in the putamen.[18] Significantly increased putamen volumes have also been reported.[9]

Although the clinical implications of structural striatal changes in schizophrenia are unresolved, caudate volume changes have been associated with illness duration and positive symptoms.[20] Also, a positive correlation was found between putamen surface contractions and affective flattening.[18]

Structural changes already observed in antipsychotic-naive schizophrenia patients are likely not because of hospitalization, chronicity or antipsychotic treatment. However, schizophrenia patients commonly have a past or present history of substance abuse or dependence. Both alcoholism[21,22] and cannabis abuse[23,24] have been associated with grey matter changes in frontal, temporal and subcortical regions as well as ventricular changes. Some studies have dealt with this issue by excluding patients with comorbid substance abuse or dependence.[25–27] However, the criteria used are not uniform among studies and encompass exclusion because of substance dependence[20], "significant abuse"[19] or abuse within a 6-month period,[28] as well as no mention of abuse.[9,10,29]

The primary aim of our study was to investigate whether the presence of hippocampal reduction, ventricular enlargement and caudate reduction is a morphologic trait in first-episode antipsychotic-naive schizophrenia patients compared with matched healthy controls. Regional voxel-wise and volumetric analyses were performed after high-dimensional intersubject warping of all patients' brains.[30] Region-of-interest (ROI) masks of the hippocampus, ventricles and caudate were created to test our a priori hypotheses. Moreover, associations with clinical measures were explored. Finally, we tested for possible effects of any lifetime substance abuse.

Methods

The study was conducted in accordance with the declaration of Helsinki II and approved by the ethics committee of the Capital Region (H-KF-01–78/97). After complete description of the study to the participants, written informed consent was obtained.

Participants

Initially, 43 patients and 43 healthy controls, matched for age, sex and parental socio-economic status, underwent MRI scans. Patients were recruited as part of a first-episode schizophrenia study conducted in the Capital Region of Copenhagen, Denmark (Psychiatric Centres Amager, Ballerup, Bispebjerg, Gentofte, Glostrup and Rigshospitalet). We included patients aged 18–45 years with a diagnosis of schizophrenia, no prior exposure to antipsychotic medication and no medical or neurologic comorbidity. The DSM-IV diagnoses were based on the Schedules for Clinical Assessment in Neuropsychiatry (SCAN), version 2.1.[31] We also included patients who used benzodiazepines (to reduce agitation and anxiety). Use of antidepressants was recorded. Patients with any lifetime substance abuse are denoted Pt_{ab}, patients with no lifetime substance abuse diagnosis are denoted $Pt_{non\text{-}ab}$ and the total patient sample is denoted Pt_{all}.

The controls were recruited from the community and had no prior or present psychiatric disorder, had never used psychotropic medication and had no first-degree relatives with a psychiatric disorder, as determined by SCAN interviews. Both patients and controls had normal physical and neurologic examinations, no history of major head injury (loss of consciousness), no mental retardation, no contraindications on MRI or any nonpsychiatric disorder. We assessed handedness by use of the Edinburgh Inventory.[32] A neuroradiologist (A.L.) examined the MRI scans, which were free of pathology. We excluded controls with substance abuse or dependence.

Clinical measures

Trained raters assessed psychopathology with the Positive and Negative Syndrome Scale (PANSS),[33] and the interviews were recorded on DVDs for validation purposes. In a random subset of 10 PANSS recordings, an intraclass correlation of 0.92 in a 2-way mixed effect model was achieved.

We defined the duration of untreated illness as the time between the first unspecific symptoms related to psychosis to the date of the MRI scan. Symptoms had to be associated with a decline in a previous stable level of function. We collected data about the duration of untreated illness with the best-estimate approach[25] with information from the SCAN interview, clinical records and relatives, if possible.

Image acquisition

We acquired high-resolution 3-dimensional (3-D) T_1-weighted, sagittal, magnetization-prepared rapid-gradient echo (MPRAGE) scans of each patient's whole head (echo time 3.93 ms, repetition time 1540 ms, inversion time 800 ms, flip angle 9°, field of view 256 mm, matrix 256×256, $1 \times 1 \times 1$ mm voxels, 192 slices) and 2-dimensional (2-D) T_2-weighted, axial, turbo spin echo (TSE) scans of the whole brain (echo time one 17 ms, echo time two 100 ms, repetition time 9000 ms, flip angle 150°, field of view 220 mm, matrix 256×256, GRAPPA acceleration factor 2, 30 reference lines, $0.9 \times 0.9 \times 3$ mm voxels, 50 slices). We used a Siemens Magnetom Trio 3-T scanner with an 8-channel head coil (Invivo Corporation).

Image processing

We corrected the images for spatial distortions owing to nonlinearity in the gradient system of the scanner[34] and processed the images using the VBM5 toolbox (http://dbm.neuro.uni-jena.de/vbm/vbm5-for spm5/) in SPM5 (Wellcome Department of Cognitive Neurology, University College London, UK), which includes a unified segmentation algorithm,[35] and a hidden Markov random field method.[36] We used the T_2-weighted images to automatically create brain masks in native space. We derived brain masked grey and white and cerebral spinal fluid tissue maps in native space from the T_1 images. We used these masks, together with the affine part of the spatial transformation from native to Montreal Neurological Institute (MNI) space, in Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra (DARTEL)[30] using default settings, allowing for high-dimensional intersubject registration. Recently, it has been shown that DARTEL can successfully register the hippocampus across patients.[37] Using the final flow fields that parameterize the deformations, brain masked grey matter, white matter and cerebral spinal fluid images were warped into average image space (DARTEL space) and modulated with the Jacobian determinant of the applied deformation fields to correct for local volume changes following the high dimensional intersubject warping. We used voxel-wise analyses to test for differences in regional tissue volume. We smoothed these tissue images with an 8-mm full-width at half-maximum Gaussian kernel. We visually checked the quality of the images generated at each processing stage.

Regions of interest

We created the following ROI masks on the average of DARTEL warped MPRAGE images for all participants. The delineation landmarks were as follows: hippocampus,[38] ventricles, lateral and third ventricle,[39] caudate nucleus, nucleus accumbens and putamen.[15]

Volumetric brain measures

We acquired intracranial volume estimates by integrating and adding image intensity values of modulated and warped grey matter, white matter and cerebral spinal fluid images. Total brain volume was acquired by integrating and adding grey matter and white matter image intensity values. Total ROI volumes were acquired to investigate whether local voxel-wise differences were reflected in whole ROI volume differences, and to generate percent difference estimates. We derived hippocampal, caudate and accumbens volume estimates by integrating image intensity values of modulated and warped grey matter images within the hippocampus, caudate and accumbens masks, respectively. We derived ventricle estimates by integrating image intensity values of modulated and warped cerebral spinal fluid images within the ventricle masks. Because the grey matter tissue of the putamen was only partially classified, we derived putamen volume estimates by integrating intensity values of modulated and warped binary image volumes within the putamen mask.

Statistical analyses

We used the Statistical Package for the Social Sciences (SPSS) to analyze demographic and volumetric data. We tested the distribution of all continuous data for normality with the Shapiro–Wilk test. Age, duration of untreated illness, cerebral spinal fluid and ventricle volumes were not normally distributed. Logarithmic transformation only normalized the distribution of duration of untreated illness. We tested age, cerebral spinal fluid and ventricle volumes nonparametrically with the Mann–Whitney U test. We tested handedness and sex differences with the Fisher exact test and socioeconomic status with the Pearson χ^2 test. Because the Pt_{ab} group only consisted of 9 patients, the Mann–Whitney U test was used to compare clinical data (PANSS scores and duration of untreated illness) between the 2 subgroups. We identified potential outliers with the Grubb outlier test.[40]

We used analysis of covariance to compare Pt_{all} and controls for volumetric estimates of intracranial volume, total brain volume, grey matter and white matter. We entered age, sex and intracranial volume as covariates. Intracranial volume was only corrected for age and sex. We used the Mann–Whitney U test to test for group differences in cerebral spinal fluid volume after the effects of age, sex and intracranial volume had been regressed out. We used the latter approach to test differences for in intracranial volume, total brain volume, grey matter, white matter and cerebral spinal fluid volumes between $Pt_{non\text{-}ab}$ and Pt_{ab}.

In the voxel-wise analyses of group differences, age, sex and intracranial volume were covariates. We first tested for differences between Pt_{all} and controls. Subsequently, planned comparisons tested for differences between $Pt_{non\text{-}ab}$ and controls, Pt_{ab} and controls, and $Pt_{non\text{-}ab}$ and Pt_{ab}. We estimated general linear models nonparametrically using Randomize, version 2.1, part of the FSL library of tools (www.fmrib.ox.ac.uk/fsl/randomise/index.html) with 10 000 permutations. We used small volume correction, applying ROI masks, to test our a priori hypotheses of hippocampal reduction, ventricle enlargement and caudate reduction. A false discovery rate threshold of 0.05 was used to correct for multiple comparisons. The clinical data (positive,

negative and total PANSS scores, and duration of untreated illness) were used as covariates in separate analyses.

We analyzed group differences in total hippocampal, ventricles, caudate, accumbens and putamen volume estimates with SPSS using a repeated-measures analysis of variance with group (Pt_{all} and control or $Pt_{non\text{-}ab}$ and control) as the between-subjects factors, and hemisphere (left and right) as the within-subjects variable. Age, sex and intracranial volume were covariates. We tested for volumetric differences of ROIs between Pt_{ab} and controls and $Pt_{non\text{-}ab}$ and Pt_{ab} by use of the Mann–Whitney *U* test, after regressing out age, sex and intracranial volume effects. We calculated the percentage ROI volume differences between groups using corrected volumes adjusted for age, sex and intracranial volume.

All tests were 2-tailed, and the significance level was set to $p < 0.05$.

Results

Demographic characteristics

Of the 43 patients with first-episode schizophrenia, we excluded 5 patients from further analyses (3 whose diagnoses were adjusted to schizotypal personality disorder and 2 with artifacts on their MRI scans). Of the 38 patients included, 9 fulfilled the DSM-IV criteria for lifetime substance abuse. Three of the 9 patients had no history of abuse for the past year, and 5 patients had no abuse for the past month. Diagnoses were based on excessive intake of alcohol ($n = 3$), cannabis ($n = 2$), alcohol and cannabis ($n = 3$) and central stimulants ($n = 1$). One patient had smoked cannabis on a few occasions in the month before the MRI scan. All participants had a negative urine screening result for substance intake. In total, there were 9 patients with any lifetime substance abuse side-diagnosis (Pt_{ab}), 29 patients with no lifetime substance abuse diagnosis ($Pt_{non\text{-}ab}$). Demographic and clinical characteristics are shown in Table 1.

There were no differences between Pt_{all} and control groups for age ($Z = -0.51$, $p = 0.61$), sex (Fisher exact test, $p > 0.99$), handedness (Fisher exact test, $p > 0.99$) and parental socioeconomic status ($\chi^2_2 = 1.85$, $p = 0.40$). Likewise, the 2 patient subgroups, Pt_{ab} and $Pt_{non\text{-}ab}$, did not differ in age, sex, handedness or parental socio-economic status ($p > 0.21$). Compared with $Pt_{non\text{-}ab}$, the Pt_{ab} group had more benzodiazepines prescribed in the investigation period (Fisher exact test, $p = 0.02$) and a tendency toward higher PANSS positive scores ($Z = -1.84$, $p = 0.07$). There was no difference in antidepressant exposure between the 2 patient groups (lifetime exposure: Fisher exact test, $p = 0.66$; current treatment: Fisher exact test, $p = 0.13$), and there was no difference between PANSS negative, PANSS total or duration of untreated illness ($p > 0.76$).

Global brain volumes

There were no volumetric differences in intracranial volume, total brain volume, grey matter, white matter or cerebral

Table 1: Demographic characteristics, clinical data and global brain volumes for antipsychotic-naive first-episode schizophrenia patients and healthy controls

Characteristic	Group; mean (SD)*			
	Pt_{ab},† $n = 9$	$Pt_{non\text{-}ab}$, $n = 29$	All patients, $n = 38$	Healthy controls, $n = 43$
Age, yr, mean (SD) [range]	28.0 (4.4) [20–35]	25.7 (5.6) [18–37]	26.2 (5.4) [18–37]	26.9 (5.7) [18–38]
Sex, male:female	6:3	20:9	26:12	30:13
Handedness, right:left, no. of patients	9:0	36:3	35:3	39:4
Parental socio-economic status, high/moderate/low, no. of patients	3/4/2	18/10/1	21/14/3	30/11/2
Benzodiazepine prescription,‡ no. of patients	8	12	20	—
Antidepressant use, lifetime, § no. of patients	3	6	9	—
Antidepressant use, current,¶ no. of patients	3	3	6	—
Positive and Negative Syndrome Scale[33] score				
Positive	21.6 (4.6)	18.5 (3.8)	19.2 (4.2)	—
Negative	21.8 (6.0)	21.8 (7.1)	21.8 (6.8)	—
Total	81.9 (16.5)	79.5 (14.9)	80.1 (15.1)	—
Duration of untreated illness, wk	188.0 (193.3)	174.5 (229.4)	178.0 (219.0)	—
Absolute, uncorrected volume, cm^3				
Intracranial	1619.7 (188.3)	1517.9 (159.9)	1542.0 (170.1)	1552.6 (124.3)
Total brain	1320.4 (155.9)	1242.1 (139.5)	1260.7 (145.3)	1271.4 (109.1)
Total grey matter	792.7 (85.3)	760.7 (79.8)	768.3 (81.1)	777.0 (64.0)
Total white matter	527.6 (74.7)	481.4 (64.9)	492.4 (69.3)	494.3 (50.9)
Cerebrospinal fluid	299.4 (53.8)	275.7 (36.3)	281.3 (41.6)	281.2 (45.9)

Pt_{ab} = patients with any lifetime DSM-IV substance abuse diagnosis; $Pt_{non\text{-}ab}$ = patients with no lifetime substance abuse diagnosis; SD = standard deviation.
*Unless otherwise indicated.
†The Pt_{ab} group comprised those with alcohol abuse, in sustained full remission ($n = 2$); alcohol abuse, on agonist therapy ($n = 1$); cannabis abuse, in a controlled environment, ($n = 1$); other abuse, sustained full remission ($n = 1$); other abuse, moderate ($n = 1$); other abuse, in a controlled environment ($n = 2$); other abuse, early partial remission ($n = 1$). Diagnoses were based on excessive intake of alcohol ($n = 3$), cannabis ($n = 2$), alcohol and cannabis ($n = 3$) and central stimulants ($n = 1$).
‡Number of patients with any prescription of benzodiazepines in the investigation period.
§Antidepressants lifetime: selective serotonin reuptake inhibitors ($n = 7$), noradrenergic and specific serotonergic antidepressant ($n = 1$), unknown antidepressant ($n = 1$).
¶Antidepressants, current: selective serotonin reuptake inhibitors ($n = 5$), noradrenergic and specific serotonergic antidepressant ($n = 1$).

spinal fluid between the Pt_{all} and control groups ($p > 0.23$) or between the 2 patient subgroups ($p > 0.14$) (Table 1).

Regional brain analyses

Results for the voxel-wise analyses are shown in Table 2. Absolute, uncorrected volume estimates for ROIs are presented in Table 3.

Hippocampus

The voxel-wise analyses revealed significant bilateral reductions in hippocampal grey matter in the Pt_{all} group as compared with the control group. This difference was accounted for by Pt_{ab} rather than by $Pt_{non\text{-}ab}$ (Fig. 1). Direct comparison of the 2 patient groups showed significantly reduced hippocampal grey matter in the Pt_{ab} group.

The results of the volumetric analyses paralleled those of the voxel-wise analysis. The significant main effect of group, Pt_{all} × control ($F_{1,76} = 4.26$, $p = 0.042$), was accounted for by Pt_{ab} (Pt_{ab} × control; $Z = –3.28$, $p = 0.001$), rather than by $Pt_{non\text{-}ab}$ ($Pt_{non\text{-}ab}$ × control; $F_{1,67} = 0.63$, $p = 0.43$). Moreover, those in the Pt_{ab} group had significantly smaller hippocampus volumes than those in the $Pt_{non\text{-}ab}$ group ($Z = –2.73$, $p = 0.006$). The comparison of Pt_{all} and control did not reveal a hemisphere × group interaction ($F_{1,76} = 2.61$, $p = 0.11$) or hemisphere effect ($F_{1,76} = 0.31$, $p = 0.58$). The group differences represented corrected hippocampal volume reductions of 2.4% between Pt_{all} and control, 6.5% between Pt_{ab} and control, and 0.1% between $Pt_{non\text{-}ab}$ and control (Fig. 2).

Ventricles

Neither the voxel-wise nor the volumetric analyses revealed ventricle differences between any of the groups ($p > 0.38$ in the volumetric analyses). Grubbs test detected one outlier in the control group. Visual inspection of this participant's MRI scan indicated no pathology or artifact. Exclusion of this outlier did not change the results. The results of exploratory analyses of group differences for the third and the lateral ventricle volumes separately were not significant.

Caudate nucleus

The voxel-wise analyses revealed significantly reduced caudate grey matter bilaterally in the Pt_{all} group compared with in the control group. This difference was primarily because of $Pt_{non\text{-}ab}$ rather than Pt_{ab} (Fig. 3) However, the 2 patient groups did not significantly differ from each other.

The analyses of caudate nucleus volume paralleled the

Table 2: Results of the voxel-wise analyses for antipsychotic-naive first-episode schizophrenia patients and healthy controls

Mask	Contrast*	Side	*Z* score	*p* value†	MNI coordinates			Cluster size, mm^3
					x	*y*	*z*	
Hippocampus	Pt_{all} < HC	Left	3.65	0.004‡	–26	–12	–28	987
		Right	3.99	0.004‡	25	–17	–25	2270
	Pt_{ab} < HC	Left	3.99	0.002‡	–26	–13	–28	1930
		Right	3.39	0.002‡	22	–14	–27	2760
	$Pt_{non\text{-}ab}$ < HC	Right	2.74	0.35	30	–17	–22	—
	Pt_{ab} < $Pt_{non\text{-}ab}$	Left	3.43	0.031‡	–24	–15	–26	1320
		Right	2.79	0.033‡	24	–10	–20	572
Ventricles	Pt_{all} > HC	Left	2.71	0.87	–28	–68	6	—
	Pt_{ab} > HC	Left	2.11	0.98	–28	–68	6	—
	$Pt_{non\text{-}ab}$ > HC	Left	3.45	0.34	–34	–51	1	—
	Pt_{ab} > $Pt_{non\text{-}ab}$	Left	2.10	0.91	–15	4	25	—
Caudate nucleus	Pt_{all} < HC	Left	3.10	0.030‡	–14	17	2	2950
		Right	2.59	0.033‡	10	17	–5	2700
	Pt_{ab} < HC	Left	2.58	0.17	–10	20	–1	—
	$Pt_{non\text{-}ab}$ < HC	Left	3.11	0.023‡	–15	–5	–25	3460
		Right	2.86	0.023‡	12	3	18	3060
	Pt_{ab} < $Pt_{non\text{-}ab}$	Left	0.93	0.93	–21	21	0	—
Nucleus accumbens	Pt_{all} < HC	Left	2.90	0.08	–12	14	–6	—
	Pt_{ab} < HC	Left	1.81	0.40	–13	14	–6	—
	$Pt_{non\text{-}ab}$ < HC	Left	3.16	0.018‡	–10	16	–7	375
		Right	2.75	0.018‡	10	14	6	168
	Pt_{ab} < $Pt_{non\text{-}ab}$	Right	0.72	0.89	14	16	–11	—
Putamen	Pt_{all} < HC	Left	2.62	0.16	–24	6	–11	—
	Pt_{ab} < HC	Right	3.08	0.099	33	3	0	—
	$Pt_{non\text{-}ab}$ < HC	Left	2.56	0.76	–14	8	–10	—
	Pt_{ab} < $Pt_{non\text{-}ab}$	Right	2.94	0.13	33	1	–1	—

HC = healthy controls; MNI = Montreal Neurological Institute; Pt_{ab} = patients with any lifetime DSM-IV substance abuse diagnosis; Pt_{all} = all patients; $Pt_{non\text{-}ab}$ = patients with no lifetime substance abuse diagnosis.
*All significant contrasts are displayed. For nonsignificant contrasts, only the voxel with the lowest *p* value is displayed.
†*p* values are false discovery rate (FDR)–corrected ($p < 0.05$).
‡Significant after FDR correction.

voxel-wise results. There was a significant main effect of group, Pt_{all} × control ($F_{1,76}$ = 8.94, p = 0.004). This group difference was primarily accounted for by $Pt_{non\text{-}ab}$ ($Pt_{non\text{-}ab}$ × control; $F_{1,67}$ = 6.88, p = 0.01), although there was a tendency toward caudate volume reduction in Pt_{ab} (Pt_{ab} × control; Z = –1.90, p = 0.06). There was no volumetric difference between the 2 patient groups (Z = –0.17, p = 0.99). There was no hemisphere × group interaction when comparing the Pt_{all} and control groups ($F_{1,76}$ = 0.62, p = 0.44) or hemisphere effect ($F_{1,76}$ = 3.24, p = 0.076). The group differences represented corrected caudate volume reductions of 5.1% between Pt_{all} and control, 5.1% between $Pt_{non\text{-}ab}$ and control, and 5.0% between Pt_{ab} and control (Fig. 4).

Nucleus accumbens and putamen

Exploratory voxel-wise analyses of the nucleus accumbens revealed a tendency for reduced grey matter in the Pt_{all} group compared with the control group. This tendency appeared to be driven by $Pt_{non\text{-}ab}$, rather than by Pt_{ab}. However, the 2 patient groups did not significantly differ from each other. Analyses of nucleus accumbens volume showed a significant main effect of group (Pt_{all} × control; $F_{1,76}$ = 6.82, p = 0.011). This group difference seemed to be accounted for by $Pt_{non\text{-}ab}$ ($Pt_{non\text{-}ab}$ × control; $F_{1,67}$ = 7.58, p = 0.008), rather than by Pt_{ab} (Pt_{ab} × control; Z = –0.88, p = 0.38).

Voxel-wise exploratory analyses of the putamen did not reveal any differences between Pt_{all} and control, $Pt_{non\text{-}ab}$ and control or Pt_{ab} and control. Exploratory analyses of putamen volume did not reveal any group main effects (Pt_{all} × control: $F_{1,76}$ = 0.42, p = 0.52; $Pt_{non\text{-}ab}$ × control: $F_{1,67}$ = 0.044, p = 0.83; Pt_{ab} × control: Z = –1.27, p = 0.20). When comparing the hemisphere × group interactions for the Pt_{all} and control groups ($F_{1,67}$ = 1.25, p = 0.27 and $F_{1,67}$ = 0.001, p = 0.97 for the accumbens and putamen, respectively). Hemisphere effects ($F_{1,67}$ = 0.18, p = 0.73 and $F_{1,67}$ = 0.012, p = 0.33 for the accumbens and putamen, respectively) were absent.

Whole brain

Exploratory voxel-wise whole brain analyses did not reveal any group differences in regional grey matter, white matter or cerebral spinal fluid volumes.

Clinical measures

Neither the voxel-wise nor the volumetric analyses revealed significant associations between PANSS scores or duration of untreated illness and hippocampal, ventricle or striatal structure volumes. However, we observed a weak tendency of longer duration of untreated illness to be associated with reduced hippocampal volume in the Pt_{all} group ($F_{1,32}$ = 2.55, p = 0.13). Associations with other brain regions, as examined with exploratory whole brain voxel-wise analyses, were absent. There were no significant associations between clinical measures and global brain measures (intracranial volume, total brain volume, grey matter, white matter or cerebral spinal fluid).

Discussion

As we had hypothesized, this study revealed significant hip-

Table 3: Absolute, uncorrected volume estimates for regions of interest for antipsychotic-naive first-episode schizophrenia patients and healthy controls

Brain region	Group; absolute, uncorrected brain volume, mm^3, mean (SD)			
	Pt_{ab}, n = 9	$Pt_{non\text{-}ab}$, n = 29	All patients, n = 38	Healthy controls, n = 43
Hippocampus				
Left	4235 (396)	4330 (390)	4307 (388)	4458 (387)
Right	4205 (424)	4260 (379)	4247 (385)	4331 (370)
Total	8440 (809)	8590 (756)	8554 (760)	8789 (717)
Ventricles				
Left	8063 (3755)	7008 (2890)	7258 (3094)	7372 (4226)
Right	7173 (2030)	6812 (3635)	6898 (3301)	7078 (4149)
Third	488 (184)	397 (140)	418 (154)	432 (147)
Total	15 725 (5508)	14217 (6267)	14574 (6058)	14882 (8112)
Caudate nucleus				
Left	3531 (370)	3374 (428)	3411 (416)	3598 (354)
Right	3611 (333)	3454 (410)	3491 (395)	3690 (368)
Total	7142 (698)	6828 (833)	6902 (805)	7288 (718)
Nucleus accumbens				
Left	358 (52)	337 (42)	342 (45)	356 (40)
Right	381 (50)	359 (38)	364 (42)	383 (39)
Total	739 (100)	697 (78)	707 (84)	739 (76)
Putamen				
Left	4117 (536)	4165 (492)	4153 (496)	4200 (376)
Right	4408 (522)	4388 (479)	4393 (482)	4444 (390)
Total	8525 (1055)	8553 (967)	8546 (974)	8643 (759)

Pt_{ab} = patients with any lifetime DSM-IV substance abuse diagnosis; Pt_{all} = all patients; $Pt_{non\text{-}ab}$ = patients with no lifetime substance abuse diagnosis; SD = standard deviation.

pocampal and caudate volume reductions in a relatively large cohort of antipsychotic-naive first-episode schizophrenia patients compared with matched healthy controls. Ventricular enlargement was absent. No differences in global volumes were found, and no significant associations between tissue volumes and psychopathology or duration of untreated illness were observed.

Our data support the growing body of evidence that indicates that the hippocampal volume is significantly reduced at the onset of schizophrenia.[3,4,6] The observed corrected volume reduction of 2.4% in the schizophrenia patients, Pt_{all}, compared with the control participants was somewhat smaller than the 8.2% reduction reported in a recent meta-analysis of data from first-episode schizophrenia patients.[4] However, the patients in the present study had never taken antipsychotics, whereas most of the studies included in the meta-analysis included medicated patients.[4] It has been suggested that previous exposure to first-generation antipsychotics may not protect against progressive reductions in hippocampal volume reduction.[8] Moreover, the meta-analysis also included studies that did not account for substance abuse or dependence. Interestingly, the hippocampal volume reduction in our study appeared most pronounced in patients with a lifetime substance abuse diagnosis (Pt_{ab}), accounting for a corrected volume reduction of 6.5% as compared with controls, whereas the reduction among patients without a history of abuse ($Pt_{non\text{-}ab}$) was only 0.1%. However, this study was not a priori designed to test for potential effects of substance abuse; thus, interpreting the results about the effects of abuse must be done cautiously.

Indeed, the absolute, uncorrected volumes (Table 3) suggest that both patient groups might have reduced hippocampal volumes compared with controls. Our findings of higher PANSS positive scores and more frequent prescriptions of benzodiazepines among the Pt_{ab} patients suggests that stress could also have influenced hippocampal volumes.[7] To our knowledge, no studies have associated benzodiazepine use with volumetric brain changes in schizophrenia. Finally, genetic variants prevalent in the normal population may contribute to morphologic variations in schizophrenia;[41] hence, the differences between the small patient subgroups observed in this study could reflect random genetic profiles rather than past substance abuse.

Our finding of reduced caudate nucleus volume agrees with studies reporting absolute[15] or significant[9,25,26,29,42,43] caudate reductions in antipsychotic-naive schizophrenia patients. Thus, our findings add to the evidence that the caudate nucleus is a key structure in the pathophysiology of schizophrenia.[44] The pathway to the observed volumetric reductions in the antipsychotic-naive state is not clear but may be attributable to decreased metabolic rates in the basal ganglia.[45] The magnitude of the caudate volume reductions in

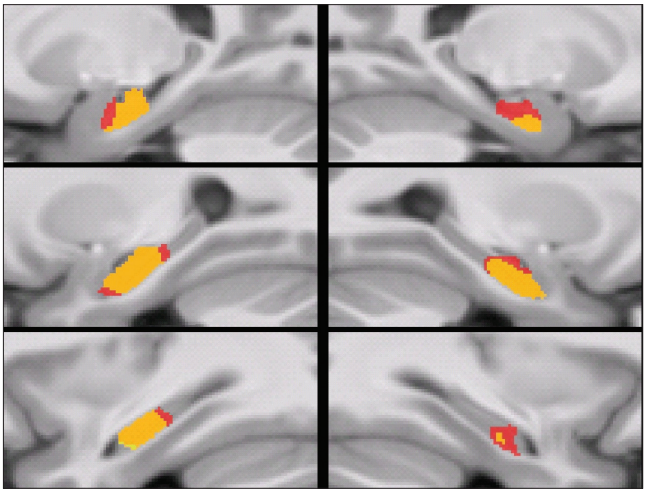

Fig. 1: Voxel-wise hippocampal grey matter volume reductions in first-episode schizophrenia patients for the right (**right, mirrored**) and left hemispheres (**left**). Voxel-wise nonparametric statistic results showing areas were all schizophrenia patients had smaller hippocampal grey matter volumes than healthy controls (yellow), areas where patients with any lifetime substance abuse had smaller volumes than healthy controls (red), and the overlap of the 2 contrasts (orange). Displayed voxels survived a false discovery rate–corrected ($p < 0.05$) small volume correction restricted to the hippocampus. Results are projected on sagittal slices of the average of all DARTEL-warped magnetization-prepared rapid-gradient echo images. From top to bottom, the images are 18, 23 and 28 mm, respectively, from the midsagittal plane.

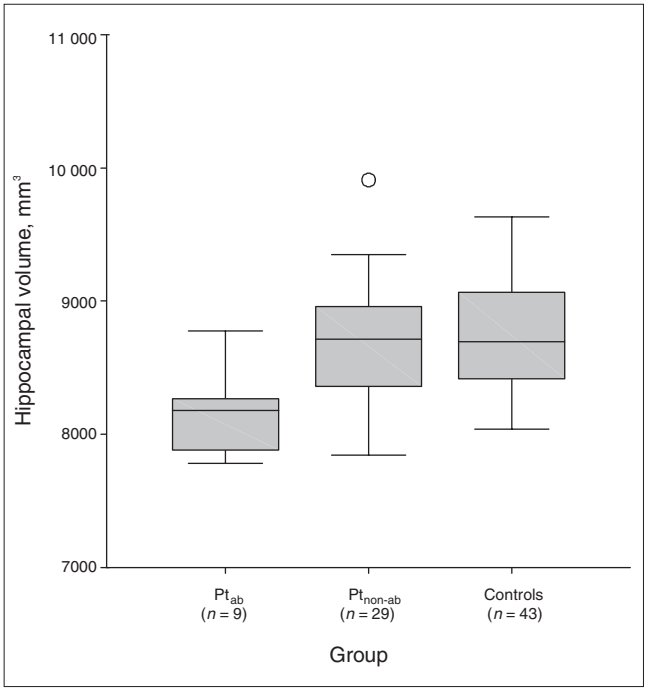

Fig. 2: Boxplot of hippocampal volumes in schizophrenia patients with any lifetime substance abuse (Pt_{ab}), patients with no lifetime substance abuse ($Pt_{non\text{-}ab}$) and matched healthy controls. Volumes are corrected for age, sex and intracranial volume. In the box-and-whisker plot, the central box represents the values from the lower to upper quartile. The transverse line in the box represents the median corrected volume. The vertical line extends from the minimum to the maximum value, excluding outside values. Outside values are defined as values smaller or larger than the lower quartile minus 1.5 times the interquartile range and are displayed as separate points (?). No outliers were identified.

this study of about 5% are in line with the average caudate reduction in the study by Glenthoj and colleagues.[15] In the present study, caudate volume reductions were significant in the $Pt_{non\text{-}ab}$ group and were also apparent in Pt_{ab}, suggesting only a modest, if any, effect of abuse on caudate volumes.

Ventricular enlargement has consistently been observed in first-episode schizophrenia[3,4] and has also been reported in antipsychotic-naive patients.[39,43] Nevertheless, ventricular enlargement was absent in the present cohort, and, as such, our data suggest that ventricular enlargement may not occur until a later stage of the disease[13] or may be related to antipsychotic medication use.[14]

In our voxel-wise analyses, the nucleus accumbens volume appeared reduced at a trend-level in the Pt_{all} group as compared with the control group. However, in the volumetric analyses, this reduction was significant. Volume reductions in the nucleus accumbens have previously been found in antipsychotic-naive schizophrenia patients,[15,18,19] but, to the best of our knowledge, significant accumbens volume reductions have not been reported. Still, limited conclusions can be drawn from our finding because it emerged from exploratory analyses. Moreover, the accumbens reductions were only partially supported by the voxel-wise analysis. In agreement with most[15,18,25,27,46] but not all[19,26] reports on the putamen, we also observed decreased absolute, uncorrected putamen volumes in patients; however, this was not significant when corrected for age, sex and intracranial volume. Only 1 study reported putamen volumes to be significantly reduced,[18] rendering the issue of structural changes in the putamen in antipsychotic-naive schizophrenia patients unresolved.

We observed no significant differences in corrected global brain volumes (intracranial volume, total brain volume, grey matter, white matter and cerebral spinal fluid) in the patients as compared with the controls. The absence of total brain volume reduction in the patients is in contrast to the findings by Steen and colleagues[4] and could reflect that some of the patients included in the meta-analysis had been exposed to first-generation antipsychotics, which may attenuate global grey matter loss.[47]

It is unclear whether reductions in the hippocampus and caudate nucleus in antipsychotic-naive schizophrenia are associated with psychopathology and illness duration. Although not significant, our observation of a weak association between longer duration of untreated illness and reduced hippocampal volume is in line with those of Matsumoto and colleagues,[11] suggesting that hippocampal changes may occur during the transition to psychosis.[48] Associations between structural abnormalities and clinical variables presumably reflect underlying pathophysiologic disturbances in neurotransmission, metabolism and genetic variance, and different mechanisms may underlie positive and negative symptoms.[49] Studies investigating the relations between volumetric measures and clinical variables have yielded inconsistent results likely attributable to differences in clinical samples, image acquisition and processing and anatomic delineation protocols.

We found no altered asymmetry between patients and

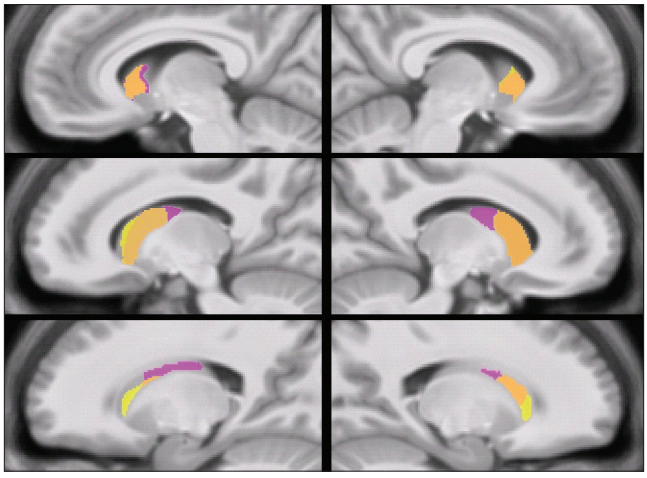

Fig. 3: Voxel-wise caudate grey matter volume reductions in patients with first-episode schizophrenia in the right (**right, mirrored**) and left (**left**) hemispheres. Voxel-wise nonparametric statistic results showing areas were all patients had smaller caudate nucleus grey matter volumes than healthy controls (yellow), areas where patients with no lifetime substance abuse diagnosis had smaller volumes than healthy controls (purple) and the overlap of the 2 contrasts (orange). Displayed voxels survived a false discovery rate–corrected ($p < 0.05$) small volume correction restricted to the caudate nucleus. Results are projected on sagittal slices of the average of all DARTEL warped magnetization-prepared rapid-gradient echo images. From top to bottom, the images are 13, 18 and 23 mm, respectively, from the midsagittal plane.

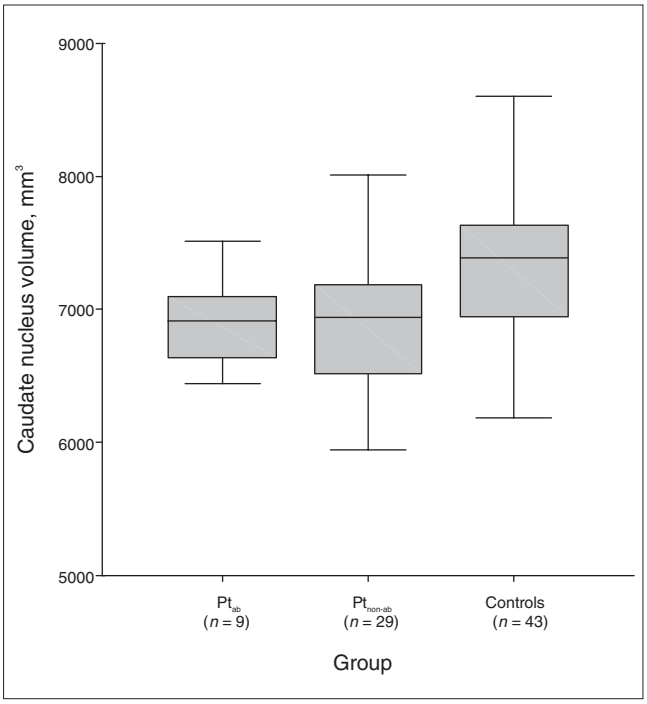

Fig. 4: Boxplot of caudate nucleus volumes in schizophrenia patients with any lifetime substance abuse (Pt_{ab}), patients with no lifetime substance abuse ($Pt_{non\text{-}ab}$) and matched healthy controls. Volumes are corrected for age, sex and intracranial volume. See Figure 2 for information about interpretation of the boxplot.

controls, hence we have not replicated our previous finding of altered asymmetry of the caudate nucleus in an independent group of 19 antipsychotic-naive patients.[15]

Limitations

The present study is limited with respect to elucidating the possible role of drug abuse on volumetric measures because it was not a priori designed to test for differences between patients with or without a lifetime substance abuse diagnosis. Moreover, even though we have assessed all DSM-IV diagnoses with a validated instrument (SCAN 2.1), we cannot exclude the possibility that some of the patients in the $Pt_{non\text{-}ab}$ group may have had a past period of excessive drug use, which we were not informed of. Additionally, because of the small number of patients with abuse and the various types of abuse, we cannot make causal inferences about the impact of lifetime substance abuse on brain structure in first-episode schizophrenia patients. Nevertheless, comorbid substance abuse has previously been associated with morphologic changes, including in the hippocampus.[22,23]

Another limitation was the unequal size of the patient subgroups. This was addressed by the use of nonparametric statistical analyses, which makes no assumptions about the distribution of the data. Notably, the volumetric analyses confirmed the differences detected by the voxel-wise analyses, hereby ruling out the possibility that the voxel-wise results were based on random local minima.

Conclusion

Our study indicates that reduced hippocampus and caudate nucleus volumes may constitute morphologic traits in first-episode antipsychotic-naive schizophrenia patients. However, the clinical implications of these findings are still unclear. Moreover, a history of substance abuse may accentuate hippocampal volume reductions. Magnetic resonance imaging studies explicitly addressing the potential effects of any lifetime substance abuse in antipsychotic-naive first-episode schizophrenia patients are warranted.

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