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Hippocampal volume reduction in male schizophrenic patients

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Abstract

Using magnetic resonance imaging of the brain, we examined volumetric measurements of total brain, hemispheres, lateral ventricles and the hippocampus/amygdala complex in male subjects (41 first-episode schizophrenics, 30 chronic schizophrenic patients and 32 healthy controls). We found significantly smaller total brain size in the chronic schizophrenic group, significantly larger lateral ventricles in both patient groups and hippocampal volume reduction bilaterally in first-episode patients (−13.2% left, −12.05% right) and chronic patients (−10.6% left, −10.5% right) compared to controls—irrespective of diagnostic subtype, family history for psychiatric diseases, psychopathology, duration of illness or age at onset.

Keywords: MRI; Schizophrenia; Hippocampus/amygdala; Brain size; Ventricular enlargement

1. Introduction

During the last decade, many studies have been reported showing structural changes in the brains of patients with schizophrenia. Magnetic resonance imaging (MRI) specifically, with improved resolution and tissue contrast, lends itself to this task, enabling more accurate estimates of volumes of brain structures. Changes in cortical volume, ventricular volume, temporal lobe structures and subcortical regions have been found thus far (e.g., Chua and McKenna, 1995; Yurgelun-Todd et al., 1996). The initial post-mortem findings of Bogerts et al. (1985) of reduction in hippocampal volume were followed by several MRI studies examining the volume of this structure. Some have found reductions of the hippocampus/amygdala complex (HAC) in schizophrenic patients (DeLisi et al., 1988; Bogerts et al., 1990, 1993; Suddath et al., 1990; Breier et al., 1992; Shenton et al., 1992; Fukuzako et al., 1996), while others (Zipursky

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et al., 1994; Kawasaki et al., 1993; DeLisi et al., 1991) have found no significant HAC-volume differences between patients and controls.

Methods differ considerably—from planimetric measures with three to five slices through the hippocampal formation to volumetric approaches using sophisticated software for data processing and measurements with decreasing slice thickness and contiguous slices.

We thus set out to study a group of male schizophrenic patients, at different stages of the illness, with an improved technique (1-mm slice thickness for HAC, 2-mm for brain size, hemispheres and lateral ventricles) and compared them to a carefully selected control group.

2. Methods

2.1. Subjects

Male patients suffering from schizophrenia and healthy male controls between 18 and 35 years of age were included in our study. We included only male subjects to increase the homogeneity of the sample by eliminating a potential confound of gender.

In the patient groups, SCID interviews were used to obtain a DSM-III-R diagnosis (Spitzer et al., 1990). Additionally, a semi-structured interview including the PANSS (Positive and Negative Symptom Scale; Kay et al., 1991), demographic data and several illness-related variables, such as education of subjects and their parents, was performed by two trained psychiatrists. As measures of duration of illness, we assessed the time in months since the first noticeable deterioration in functioning, number of months since the first appearance of positive psychotic symptoms, and months since the first hospitalization. We also determined if patients had a family history of psychiatric disorders. This was accomplished by clinical interviews of patients and their relatives. The patients consisted of a first-episode (FE) and a chronic schizophrenic (CS) sample. They were re-evaluated at least 1.5–2 years after the first assessment to confirm the diagnosis—especially important for the first-episode group. The patients in the first-episode group were examined and scanned during the first week of their hospitalization. They had received neuroleptic treatment for a maximum of 1 week. All patients were treated at the Department of Psychiatry, University of Innsbruck, Austria.

The control group consisted of employees recruited from our hospital and male nurse-trainees. Controls also received a semi-structured interview and were matched to the patient group with respect to age, height and parental education. A history of substance dependence or abuse or of a serious medical or neurological illness were exclusion criteria in both patient and control groups. None of the controls had a family history of psychiatric disorder. Informed consent for participation in this study was obtained from all subjects after a complete description of the study and an explanation of its aims.

2.2. MR-image acquisition

MRI was performed on a 1.5-T whole-body system (Magnetom VISION, Siemens, Germany) using a conventional circular polarized head coil. A standard 3-D MP-RAGE sequence (TR = 9.7 ms, TE = 4 ms, a = 12°) was used to obtain T1 weighted images of the brain (Mugler and Brookeman, 1991). This sequence allows a good delineation between cerebrospinal fluid (CSF) and parenchymal structures and differentiation of gray and white matter. Between 128 and 150 contiguous slices in a sagittal orientation were acquired with an in-plane resolution of 0.9 mm and a slice thickness of between 0.9 and 1.4 mm. Thus, nearly isotropic 3-D MR data sets were obtained, making highly accurate volumetric MR measurements possible. After image acquisition, the MR images were transferred to an external workstation for image processing.

2.3. Image processing and volume measurement

Volume meaurements were performed on a commercially available workstation (Allegro; ISG Technologies, Canada). With the Allegro software package, volume measurements are typically performed using a combination of thresholding,

region growing and manual tracing (Brant-Zawadzki et al., 1993). A threshold is used to discriminate structures in high-contrast portions of the images. By placing a seed point, the anatomical region of interest within the selected range of gray values is then identified by region growing. Because of ambiguous gray levels, partial volume effects and MRI artifacts, manual editing is usually necessary to explicitly define the brain regions of interest within the image. Seed points placed in one image can be automatically propagated to consecutive slices. This enables an interactive, semi-automatic segmentation, with the rater previewing and, when necessary, editing each individual image for an accurate delineation of the respective anatomy.

After careful segmentation of the anatomy of interest, the respective volume is automatically calculated by counting the number of voxels contained within the segmented structure. The number of voxels counted is subsequently multiplied with the individual voxel volume, taking into account minor differences in slice thickness and in-plane resolution of different MR data.

For the particular case of the hippocampus/amygdala complex and the other structures which were assessed in our study, segmentation is best performed on coronal slices. Before segmentation, the original MR images in sagittal orientation were thus reformatted into contiguous coronal slices with 1-mm slice thickness.

2.4. Neuroanatomical delineation

Measurements of the hippocampus–amygdala complex were performed following the method developed by Bogerts et al. (1990)—starting posteriorly at the level where the fornix surrounding the pulvinar is interrupted by the coronal sections. As a definite separation between hippocampus and amygdala was not possible, we measured both in one structure that was then divided into a posterior and an anterior portion. The posterior/hippocampal portion extends from the fornix/pulvinar slice to the slice just posterior to the level of the mammillary bodies, including the slice immediately posterior, and contains mainly hippocampal tissue. The anterior/amygdala portion reaches from the mammillary body slice to the slice where the amygdaloid complex loses its typical oval shape and consists mainly of amygdala tissue.

The lateral ventricles were measured on coronal slices without determining different subdivisions.

The whole brain measurement includes both hemispheres, the brainstem and the cerebellum. The medulla is separated from the spinal cord by a line between the caudal ends of the bulb of the medulla.

The measurements of the different brain regions were performed by a single, trained rater (M.H.), who was blind to group membership. To assess intra-rater reliability of the volumes obtained, volumetric measurements of the lateral ventricles and the hippocampus/amygdala complex were carried out twice for 10 patients/volunteers. Each data set was individually processed twice, the time between two successive sessions being 3–4 months. With this method we obtained an intra-rater variability of >0.99 for the lateral ventricles, 0.98 for hemispheres and 0.907 for the hippocampus/amygdala complex.

2.5. Statistical methods

All computations were performed with the statistical package SPSS for Windows, version 6.0. Estimates of volumes of left and right hippocampus/amygdala, hemispheres and lateral ventricles were adjusted with respect to age, height and total brain volume using multiple linear regression with backward variable elimination. Adjusted values were obtained by replacing the actual covariate values by their population means in the regression equation.

Comparisons between the groups (first-episode, chronic schizophrenia, controls) with respect to adjusted brain volumetric measurements and laterality indices were made using the Mann–Whitney U test. No adjustments for multiple comparisons were made (Rothman, 1990). Pearson correlation coefficients were used to determine associations between volumetric brain measures and clinical variables (PANSS subscores, age at onset, duration of illness, diagnostic subtypes). Throughout, results were considered statistically significant when the corresponding p-value was 0.05 or less, by two-tailed analysis.

3. Results

We examined 41 first-episode patients, 30 chronic schizophrenic patients and 32 healthy controls. See Table 1 for demographics, illness variables and diagnostic subtypes according to DSM-III-R. All subjects were male, Caucasian and right-handed. Table 2 shows the raw/adjusted brain volume data for all three groups.

3.1. Total brain volume

For the total brain volume, we found that the chronic schizophrenic group had significantly smaller volumes compared to controls ($p=0.009$). There were no differences between first-episode patients and controls, and only trend level differences between first-episode and chronic patients ($p=0.078$). The chronic schizophrenic group had a 5.2% smaller total brain size than the controls.

3.2. Hemispheres

There were no significant differences between FE patients and controls, but CS patients had significantly smaller hemisphere volumes on both sides compared to controls ($p=0.001$ on the left, $p=0.003$ on the right) and to FE patients ($p=0.008$ left, $p=0.019$ right).

3.3. Lateral ventricles (see Fig. 1)

Lateral ventricles were significantly larger in first-episode patients compared to controls ($p<0.001$ left ventricle, $p=0.004$ right ventricle) and in chronic schizophrenic patients compared to controls ($p<0.001$ left ventricle, $p=0.001$ right ventricle). Expressing the difference in volume in percentages, the FE patients had a 76.5% increase on the left side and a 60.5% increase on the right side compared to healthy controls. The figures for the CS group were 144.8% for the left lateral ventricle and 66.6% for the right side.

The difference between FE and CS showed a tendency towards statistical significance on the left ($p=0.071$), but was not significant on the right side.

3.4. Posterior/hippocampal portion of the HAC (see Fig. 2)

The posterior/hippocampus portion was significantly smaller in first-episode patients compared to controls ($p=0.001$ left, $p=0.009$ right hippo-

Table 1
Sample characteristics (means; standard deviations in parentheses)

	First-episode patients $n=41$	Chronic patients $n=30$	Healthy controls $n=32$
Age (years)	24.5 (4.7)	28.3 (4.5)	30.5 (5.8)
Height (cm)	176.4 (5.5)	177.8 (5.9)	178.1 (7.4)
Education (years)	10.9 (2.0)	10.4 (2.2)	11.6 (2.6)
Parental education (years)	10.7 (3.3)	11.9 (3.7)	9.8 (1.8)
Months since:			
1st hospitalization	0.7 (2.0)	70.1 (49.9)	
1st positive symptoms	8.3 (17.7)	93.7 (72.6)	
1st deterioration of functioning	19.6 (26.4)	103.2 (74.6)	
Diagnostic subtypes according to DSM-III-R (%)			
Disorganized (295.1 ×)	7.3	6.7	
Catatonic (295.2 ×)	2.4	3.3	
Paranoid (295.3 ×)	4.9	3.3	
Schizophreniform (295.4 ×)	14.6		
Residual (295.6 ×)		33.3	
Undifferentiated (295.9 ×)	70.7	53.3	

Table 2
Brain measurements: comparison of first-episode (FE) and chronic schizophrenics (CS) with healthy controls[a]

		FE ($n=41$)	CS ($n=30$)	Controls ($n=32$)
Total brain volume		1220.6±118.2 *1210.2±119.2*	1180.2±89.6 *1182.5±89.0***	1236.4±88.9 *1246.7±84.2*
Hemisphere	left	524.3±53.6 *520.2±53.9*	494.0±46.7 *494.9±47.2***†	533.2±39.6 *537.2±36.9*
	right	526.7±50.1 *522.6±50.5*	500.3±46.8 *501.3±46.8***†	531.7±38.0 *535.7±35.4*
Lateral ventricle	left	4.77±2.85 *4.96±2.97****	7.02±4.98 *6.88±4.66***(†)*	2.99±1.60 *2.81±1.49*
	right	4.63±2.72 *4.99±2.95***	5.34±2.92 *5.18±2.70***	3.46±1.92 *3.11±1.65*
Hippocampus	left	2.46±0.43 *2.45±0.38***	2.47±0.52 *2.52±0.52(*)*	2.86±0.53 *2.82±0.51*
	right	2.43±0.38 *2.42±0.35***	2.41±0.38 *2.46±0.36**	2.79±0.69 *2.75±0.66*
Amygdala	left	2.07±0.45 *2.06±0.42*	1.97±0.35 *2.01±0.36*	2.10±0.50 *2.07±0.51*
	right	2.12±0.52 *2.11±0.49*	2.09±0.60 *2.14±0.59*	2.20±0.52 *2.17±0.52*
HAC (hippocampus amygdala complex)	left	4.53±0.63 *4.51±0.52***	4.44±0.62 *4.53±0.63**	4.96±0.73 *4.89±0.71*
	right	4.55±0.67 *4.53±0.58***	4.50±0.83 *4.59±0.80**	4.99±0.92 *4.92±0.89*

[a]Raw mean±SD (cm^3), with adjusted mean±SD in italics. Total brain volume and hemispheres adjusted for age and height; hippocampus, amygdala and ventricles also adjusted for total brain volume.
All statistical tests are based on adjusted brain measures. *Significantly different from control group: $*p<0.05$, $**p<0.01$, $***p<0.001$, $^{(*)}p<0.10$. †Significantly different from FE group: $^{\dagger}p<0.05$, $^{(\dagger)}p<0.10$.

campus). For the difference between CS and controls $p=0.055$ on the left and $p=0.031$ on the right. There was no difference between FE and CS and, taken together, the posterior/hippocampal portion was significantly smaller in schizophrenic patients than in controls ($p=0.006$ right, $p=0.002$ left). The mean volume reduction was 13.1% (left) and 12.0% (right) for the FE group and 10.6% (left) and 10.5% (right) for the chronic schizophrenic patients.

3.5. Anterior/amygdala portion of the HAC

The volume of the anterior/amygdala portion showed no statistically significant differences between the three groups.

3.6. Total hippocampus–amygdala complex (HAC)

This structure consisted of the posterior/hippocampal portion and the anterior/amygdala

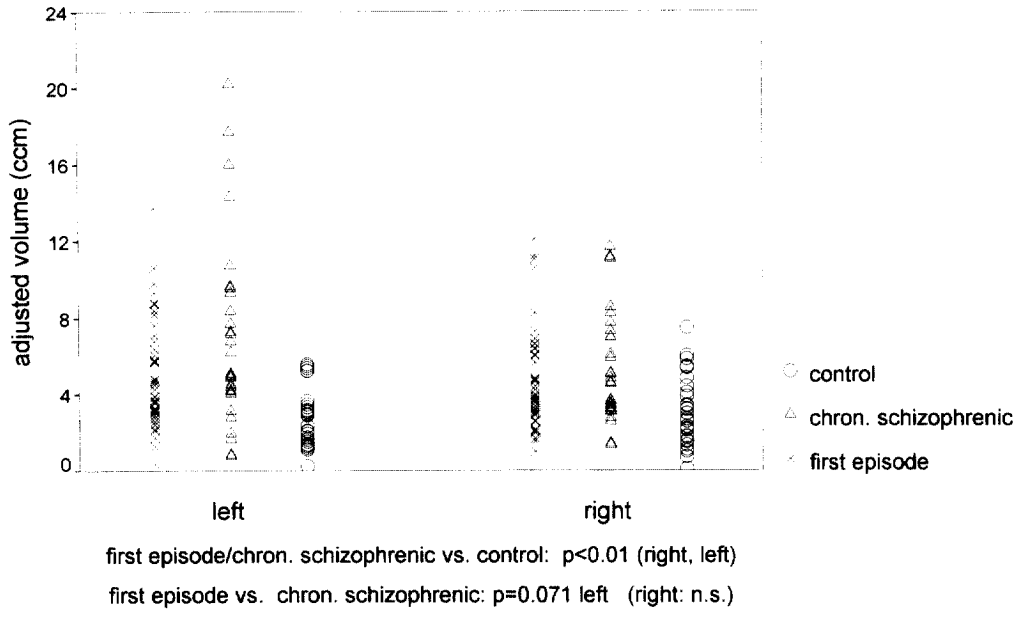

Fig. 1. Lateral ventricle: first episode vs chronic schizophrenic vs control.

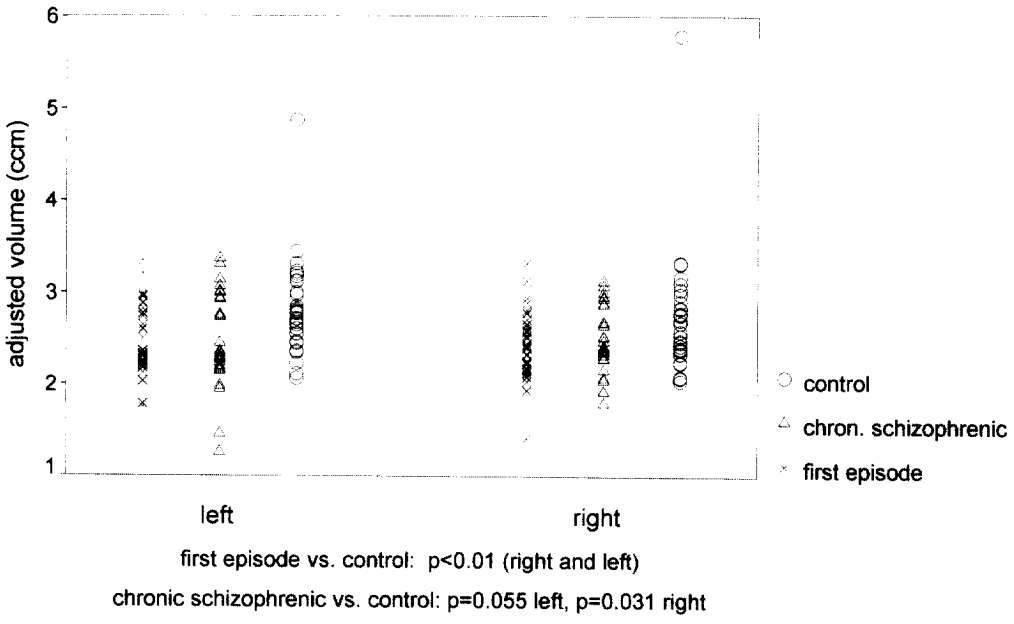

Fig. 2. Posterior portion of hippocampus/amygdala complex: first episode vs chronic schizophrenic vs control.

portion taken together. Both schizophrenic groups showed significantly smaller HAC volume (left: $p<0.0054$; right: $p<0.0074$) than the control group. There was no significant difference between the two patient groups.

3.7. Clinical variables

We could not find a correlation between any of the clinical variables, such as the three different determinations of duration of illness, positive and negative PANSS subscores, total PANSS score, a positive family history for psychiatric disorders and the different brain regions anlayzed.

4. Discussion

This direct comparison of MR-volumetric data of different brain regions of first-episode (FE), chronic schizophrenic patients (CS) and controls yielded several interesting results.

We found a highly significant reduction of total brain volume in the group of chronic schizophrenic patients, but failed to see a difference between FE patients and healthy controls. Our results add to the information generated by the meta-analysis of brain and cranial size by Ward et al. (1996). This group found a small but also highly significant reduction of brain and intracranial size in schizophrenia, yet no decrease of extracranial measures.

In our study brain volume differences become even more pronounced when restricting measurements to the hemispheres: CS patients had significantly smaller hemispheres bilaterally, not only compared to controls but also to FE schizophrenic patients. In accordance with our results, Nopoulos et al. (1995) also found no difference in total brain volume when comparing first-episode patients and controls, although they detected a significant increase of total CSF in the patient group.

In this context, McNeil et al. (1993) found a significant reduction in head circumference among preschizophrenic infants as compared to a matched control group from the same delivery series. DeLisi et al. (1995), in a prospective study of FE patients with follow-up MR scans after 4 years, reported a decrease in both cerebral hemispheres over time. This did not correlate with pharmacological treatment. There was no significant structural change in the control group.

An enlargement of the ventricles is one of the most robust results of morphometric studies in schizophrenic patients carried out over the past decades (Hecker, 1871; Haug, 1962; Johnstone et al., 1976; Suddath et al., 1990; DeLisi et al., 1991, 1992; Degreef et al., 1992; Andreasen et al., 1994). In our study, the FE as well as the CS group showed highly significant increases in lateral ventricle volume bilaterally when compared to controls. The mean volume increase of the FE group was between the CS and the control group. We could not detect a correlation with age or the onset of illness. In a study comparing FE and CS with neurological controls—apart from our results the only other report directly comparing FE to CS and controls—DeLisi et al. (1991) found larger left lateral ventricles in FE compared to controls. The left ventricles of CS were significantly larger than those of the FE patients. In their prospective 4-year follow-up study, DeLisi et al. (1995) reported a significant increase in the volume of the left lateral ventricles of FE patients over time after correcting for total brain size. Rapoport et al. (1996), when rescanning childhood-onset schizophrenic patients after 2 years, found a highly significant increase in lateral ventricular volume in this schizophrenic subgroup compared to controls. These two studies are both suggestive of a degenerative process.

In our study, the posterior/hippocampal portion of the HAC was significantly smaller bilaterally in FE as compared to controls. Comparing CS to controls, statistical significance is evident ($p=0.031$) on the right side, while a trend in the same direction is seen for the left side ($p=0.055$). This is most likely a power problem, given the smaller number of patients in the CS group. FE and CS do not differ significantly in the posterior/hippocampal portion.

Reductions in HAC volumes were not correlated with any of the clinical measures. Our results are in agreement with those of several other groups (Bogerts et al., 1990, 1993; Breier et al., 1992; Shenton et al., 1992). Suddath et al. (1990) also reported a bilateral hippocampal volume reduction

in their sophisticated study with 15 pairs of monozygotic twins discordant for schizophrenia. They stated that—when appropriate controls are available—these subtle structural abnormalities can be observed in the majority of schizophrenic patients and are most likely characteristic of the disease. Fukuzako et al. (1996) described not only a bilateral volume reduction for the hippocampal formation, but found also a bilateral shortening of this structure in chronic schizophrenic patients.

In contrast to earlier results describing a volume reduction predominantly on the left (Bogerts et al., 1990; Shenton et al., 1992), we could not detect a trend towards laterality, which is in accordance with more recent work (Suddath et al., 1990; Bogerts et al., 1993; DeLisi et al., 1995; Fukuzako et al., 1996).

Two studies—those of Zipursky et al. (1994) and Kawasaki et al. (1993)—did not show differences in hippocampal volume between schizophrenic patients and controls. Both investigated smaller patient samples, measured thicker slices and employed a different delineation of the temporal structures. These methodological differences might account for the inconsistency of the reported findings with some of the other studies mentioned above.

In other areas of the brain, the influence of pharmacological agents (i.e., antipsychotics) on morphometric measures (i.e., caudate and putamen volumes) has been described by several groups (Keshavan et al., 1994; Chakos et al., 1994, 1995; Frazier et al., 1996). Rodriguez et al. (1996) presented results of the effect of cumulative neuroleptic exposure on caudate nuclei, putamen and hippocampus volumes and reported a main effect of neuroleptic exposure on caudate and putamen volumes, but no significant effect on hippocampus volumes. Their results seem to make it unlikely that neuroleptics influence hippocampal volume.

Putting all of the available evidence in perspective and considering the complexity and heterogeneity of the disease, we hypothesize that the pathological mechanism underlying morphological changes in the brains of schizophrenic patients could be caused by two different etiological processes: one that is a developmental defect, resulting in a volume reduction of the hippocampal structure and a second one that is of a progressive nature and leads to continuing enlargement of the lateral ventricles and a reduction of cortical gray matter.

Further information from long-term studies of the relevant brain structures is needed to test this hypothesis.

References

Andreasen, N.C., Flashman, L., Flaum, M., Arndt, S., Swayze II, V.W., O'Leary, D.S., Ehrhart, J.C., Yuh, W.T.C., 1994. Regional brain abnormalities in schizophrenia measured with magnetic resonance imaging. J. Am. Med. Assoc. 272, 1763–1769.

Bogerts, B., Meertz, E., Schönfeldt-Bausch, R., 1985. Basal ganglia and limbic system pathology in schizophrenia. Arch. Gen. Psychiatry 42, 784–791.

Bogerts, B., Ashtari, M., Degreef, G., Alvir, J.M.J., Bilder, R.M., Lieberman, J.A., 1990. Reduced temporal limbic structure volumes on magnetic resonance images in first episode schizophrenia. Psychiatry Res. 35, 1–13.

Bogerts, B., Lieberman, J.A., Ashtari, M., Bilder, R.M., Degreef, G., Lerner, G., Johns, C., Masiar, S., 1993. Hippocampus–amygdala volumes and psychopathology in chronic schizophrenia. Biol. Psychiatry 33, 236–246.

Brant-Zawadzki, M.N., Gillan, G.D., Atkinson, D.J., 1993. Three-dimensional MR imaging and display of intracranial disease: improvements with the MP-RAGE sequence and gadolinium. J. Magnet. Reson. Imaging 3, 656–662.

Breier, A., Buchanan, R.W., Elkashef, A., Munson, R.C., Kirkpatrick, B., Gellad, F., 1992. Brain morphology and schizophrenia. Arch. Gen. Psychiatry 49, 921–926.

Chakos, M., Lieberman, J.A., Bilder, R.M., Bornstein, M., Lerner, G., Bogerts, B., Wu, H., Konon, B., Ashtari, M., 1994. Increase in caudate nuclei volumes of first episode schizophrenic patients taking antipsychotic drugs. Am. J. Psychiatry 151, 1430–1436.

Chakos, M., Lieberman, J.A., Alvir, J.M.J., Bilder, R.M., Ashtari, M., 1995. Caudate nuclei volumes in schizophrenic patients treated with typical antipsychotics of clozapine. Lancet 345, 456–457.

Chua, S.E., McKenna, P.J., 1995. Schizophrenia—a brain disease? A critical review of structural and functional cerebral abnormality in the disorder. Br. J. Psychiatry 166, 563–582.

Degreef, G., Ashtari, M., Bogerts, B., Bilder, R.M., Jody, D.N., Alvir, J.M.J., Lieberman, J.A., 1992. Volumes of ventricular system subdivisions measured from magnetic resonance images in first-episode schizophrenic patients. Arch. Gen. Psychiatry 49, 531–537.

DeLisi, L.E., Dauphinais, I.D., Gershon, E.S., 1988. Perinatal complications and reduced size of brain limbic structures in familial schizophrenia. Schizophr. Bull. 14, 185–191.

DeLisi, L.E., Hoff, A.L., Swartz, J.E., Shields, G.W., Halthare, S.N., Gupta, S.M., Henn, F.A., Anand, A.K., 1991. Brain

morphology in first-episode schizophrenic-like psychotic patients: a quantitative magnetic resonance imaging study. Biol. Psychiatry 29, 159–175.

DeLisi, L.E., Stritzke, P., Riordan, H., Holan, V., Boccio, A., Kushner, M., McClelland, J., Van Eyl, O., Anand, A., 1992. The timing of brain morphological changes in schizophrenia and their relationship to clinical outcome. Biol. Psychiatry 31, 241–254.

DeLisi, L.E., Tew, W., Xie, S.H., Hoff, A.L., Sakuma, M., Kushner, M., Lee, G., Smith, A.M., Shedlack, K., Grimson, R., 1995. A prospective follow-up study of brain morphology and cognition in first-episode schizophrenic patients: preliminary findings. Biol. Psychiatry 38, 349–360.

Frazier, J., Giedd, J., Kaysen, D., Albus, K., Hamburger, S., Alaghband Rad, J., Lenane, M., McKenna, K., Breier, A., Rapoport, J., 1996. Childhood-onset schizophrenia: brain MRI rescan after 2 years of clozapine maintenance treatment. Am. J. Psychiatry 153, 564–566.

Fukuzako, H., Fukuzako, T., Hashiguchi, Y., Takeuchi, K., Kirakawa, K., Ueyama, K., Takigawa, M., Kajiya, Y., Nakajo, M., Fujimoto, T., 1996. Reduction in hippocampal formation volume is caused mainly by its shortening in chronic schizophrenia: assessment by MRI. Biol. Psychiatry 39, 938–945.

Haug, J.O., 1962. Pneumoencephalographic studies in mental disease. Acta Psychiatr. Scand. (Suppl.). 1 114.

Hecker, E., 1871. Die Hebephrenie. Arch. Pathol. Anat. Physiol. Klin. Med. 52, 394–409.

Johnstone, E.C., Crow, T.J., Firth, C.D., Husband, J., Kreel, L., 1976. Cerebral ventricular size and cognitive impairment in chronic schizophrenia. Lancet 2, 924–926.

Kawasaki, Y., Maeda, Y., Urata, K., Higashima, M., Yamaguchi, N., Suzuki, M., Takashima, T., Ide, Y., 1993. A quantitative magnetic resonance imaging study of patients with schizophrenia. Eur. Arch. Psychiatry Clin. Neurosci. 242, 268–272.

Kay, S.R., Opler, L.A., Fiszbein, A. (Eds.), 1991. Positive and Negative Syndrome Scale (PANSS) rating manual. Multi-Health, Ontario.

Keshavan, M., Bagwell, W., Haas, G., Sweeney, J., Schooler, N., Pettegrew, J., 1994. Changes in caudate volume with neuroleptic treatment. Lancet 344, 1434

McNeil, T.F., Cantor-Graae, E., Nordström, L.G., Rosenlund, T., 1993. Head circumference in 'preschizophrenic' and control neonates. Br. J. Psychiatry 162, 517–523.

Mugler, J., Brookeman, J., 1991. Rapid three-dimensional T1-weighted MR imaging with the MP-RAGE sequence. J. Magnet. Reson. Imaging 1, 561–567.

Nopoulos, P., Torres, I., Flaum, M., Andreasen, N.C., Ehrhardt, J.C., Yuh, W.T.C., 1995. Brain morphology in first-episode schizophrenia. Am. J. Psychiatry 152, 1721–1723.

Rapoport, J.L., Alaghband-Rad, J., Jacobsen, L.K., Giedd, J.N., 1996. Childhood onset schizophrenia: anatomic brain MRI. Poster presentation at the 35th Annual Meeting of the American College of Neuropsychopharmacology, 9–13 December, Puerto Rico.

Rodriguez, R., Gupta, S., Andreasen, N., 1996. The effect of cumulative neuroleptic exposure on caudate and putamen volumes. Poster presentation at the 35th Annual Meeting of the American College of Neuropsychopharmacology, 9–13 December, Puerto Rico

Rothman, K.J., 1990. No adjustments are needed for multiple comparisons. Epidemiology 1, 43–46.

Shenton, M.E., Kikinis, R., Jolesz, F.A., Pollak, S.D., LeMay, M., Wible, C.G., Hakama, H., Martin, J., Metcalf, D., Coleman, M., McCarley, R.W., 1992. Abnormalities of the left temporal lobe and thought disorder in schizophrenia. N. Engl. J. Med. 327, 604–612.

Spitzer, R., Williams, J., Gibbon, M., First, M., 1990. Structured clinical interview for DSM III-R-patient. SCID-P. Version 1.0. American Psychiatric Press, Washington DC.

Suddath, R.L., Christison, G.W., Torrey, E.F., Casanova, M.F., Weinberger, D.R., 1990. Anatomical abnormalities in the brains of monozygotic twins discordant for schizophrenia. N. Engl. J. Med. 322, 789–794.

Ward, K.E., Friedman, L., Wise, A., Schulz, S.C., 1996. Meta-analysis of brain and cranial size in schizophrenia. Schizophr. Res. 22, 197–213.

Yurgelun-Todd, D.A., Kinney, D.K., Sherwood, A.R., Renshaw, P.F., 1996. Magnetic resonance in schizophrenia. Semin. Clin. Neuropsychiatry 1, 4–19.

Zipursky, R.B., Marsh, L., Lim, K.O., DeMent, S., Shear, P.K., Sullivan, E.V., Murphy, G.M., Czernansky, J.G., Pfefferbaum, A., 1994. Volumetric MRI assessment of temporal lobe structures in schizophrenia. Biol. Psychiatry 35, 501–516.