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Hippocampal volume asymmetry and age at illness onset in males with schizophrenia

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Abstract To determine whether there are disturbances of hippocampal volume asymmetry in schizophrenic patients, we obtained contiguous, 1-mm-thick magnetic resonance images in 28 males with chronic schizophrenia and in 28 age-matched healthy males. The schizophrenic patients showed a bilateral reduction in volume of the hippocampal formation (HF; left 7.0%; right 8.7%). This reduction was significantly associated with the severity of disorganization syndrome ($P < 0.0005$). A significant asymmetry in the HF volume was found in the control subjects ($P = 0.006$), but not in the patients ($P = 0.40$). There was a significant positive correlation between the asymmetry index and the patient's age at the onset of schizophrenia ($r = 0.46$, $P = 0.01$). Results indicate that a disturbance in the normal asymmetry of the HF may be a characteristic in schizophrenia, particularly in patients with an early onset of the illness.

Key words Hippocampal formation · Asymmetry · Magnetic resonance imaging · Onset · Schizophrenia

Introduction

The hypothesis that a disturbance of cerebral lateralization exists in patients with schizophrenia has been investigated by various methods. Recent technical developments in magnetic resonance imaging (MRI) now enable assessment of morphologic asymmetry in the brain structures in vivo. A reduction or reversal of such asymmetry has been demonstrated in several brain structures of patients with schizophrenia (Becker et al. 1990; Crow 1990; Falkai et al. 1992; Bilder et al. 1994; Petty et al. 1995; Weinberger 1995; Jacobsen et al. 1996).

Various morphologic abnormalities have been documented in the medial temporal lobe of schizophrenic patients (Chua and McKenna 1995). Two reports have documented the morphologic asymmetry of this structure (Becker et al. 1990; Jacobsen et al. 1996). Becker et al. reported a reversal of the right-left asymmetry in the volume of the hippocampal formation (HF) in contrast to such structures as the temporal lobe and the parahippocampal gyrus in schizophrenic patients as well as in healthy subjects. However, those preliminary findings were discounted because of the small sample size and the disadvantages inherent in the planimetric method. The report by Jacobsen et al. showed a lack of normal hippocampal asymmetry in patients who had the onset of schizophrenia by age 12 years. However, the researchers did not differentiate the HF from the amygdala; thus, their estimation of hippocampal asymmetry may have been influenced by the loss of the anterior hippocampus. We recently reported a highly reliable method for measuring the volume of the HF (Fukuzako et al. 1996). The main objective of the present study was to evaluate the findings of Becker et al. (1990) and Jacobsen et al. (1996) in a larger sample using an advanced morphometric technique of MRI.

Subjects and methods

We studied 28 Japanese male patients (mean age 36.6 ± 6.3 years) with the following characteristics: (a) met the DSM-III-R criteria for schizophrenia; (b) were below the age of 45 years; (c) had no history of neurologic disorders, metabolic disorders, drug abuse, or alcoholism; and (d) had not received electroconvulsive therapy. Their mean age when the first positive psychotic symptoms appeared was 22.9 ± 5.9 years. They were receiving neuroleptics (518.9 mg/day of chlorpromazine equivalents) at the time of the MRI scan.

The control group consisted of 28 age-matched healthy Japanese male volunteers (mean age 37.0 ± 5.1 years) who were recruited from among the hospital staff and their relatives. None had a history of psychiatric or neurologic illness or of alcohol or drug abuse. The two groups of subjects were not completely matched for educational level (schizophrenics vs controls: 13.7 ± 7.3 vs

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14.9 ± 4.0 years; t = 1.90, P = 0.07). All subjects were right-handed, as determined by the Edinburgh Inventory (Schachter et al. 1987). Each subject gave informed consent to participate in the study. Two trained neuropsychiatrists (K.Y. and T.F.) evaluated the patients using the Scale for the Assessment of Negative Symptoms (SANS) and the Scale for the Assessment of Positive Symptoms (SAPS; Andreasen 1984a, b). The score employed for each item was the average score given by the two raters. The average scores were 51.6 ± 23.2 on the SANS and 28.8 ± 19.9 on the SAPS.

The methods used to acquire and process MRI data were similar to those we previously described (Fukuzako et al. 1996). The MRI examinations were performed using a Siemens MR unit (Magnetom H15, Siemens Erlangen, Germany) operating with a 1.5-Tesla magnetic field. Using a fast-low-angle-shot sequence, we collected 256 sagittal slices, 1 mm thick, through the entire head. Images were transferred to a workstation connected to the MR unit. To measure HF bilaterally, we reconstructed on the workstation console coronal images perpendicular to the long axis of the left sylvian fissure. These images were printed on paper with a videoprinter (VP-3500, Seikosha, Tokyo, Japan). Two different neuropsychiatrists (H.F. and S.K.) traced the boundary of the HF on the print with the use of a digitizing tablet (SD-421, Wacom, Tokyo, Japan). The HF region outlined in this study included the hippocampus, dentate gyrus, fimbria, alveus, and subiculum. Demarcation of the hippocampus from the amygdala was made by detection of the alveus (Cook et al. 1992). As previously demonstrated, we achieved a good test-retest reliability for measurements of the HF volume. The HF volumes were adjusted for total intracranial volume (TICV; Jack et al. 1989).

To investigate the relationships between the degree of hippocampal asymmetry and the patient's age at the onset of illness, the duration of the illness and the clinical symptoms, an asymmetry index was calculated by using the formula (R – L)/0.5 * (R + L), where R is the HF volume on the right and L is that on the left side.

Table 1 Factor analysis of symptom scores

	Factor 1 Psychomotor poverty	Faktor 2 Disorganization syndrome	Factor 3 Reality distortion
Alogia	0.88		
Affective flattening	0.85		
Anhedonia–asociality	0.74		
Avolition–apathy	0.69		
Inappropriate affect		0.79	
Positive formal thought disorder		0.70	
Bizarre behavior		0.65	
Hallucinations			0.95
Delusions			0.71

NOTE: Rotated factor matrix of loadings on all three factors with Eigen values greater than unity following factor analysis of symptom scores derived from SANS and SAPS. Loadings of less than 0.5 are omitted for clarity. The corresponding subsyndrome is given for each factor

Analyses were performed with the Statistical Analysis System (SAS). The symptom ratings entered into the factor analysis were the scores for ten items on the SANS and SAPS. Principal component extraction of the factors was followed by VARIMAX rotation. Factor subsyndrome scores were calculated by the regression method. Multivariate analysis of variance (MANOVA) with a between-subject factor of diagnosis (schizophrenics vs controls) and a within-subject factor of side (left vs right) was applied to the HF volumes, followed by a post hoc t-test. Paired t-tests were used to test the symmetry of the left and right HF. Pearson's product moment (r) or Kendall's rank correlation coefficient (τ) was used to determine the relationship between the two kinds of values. A level of $P < 0.05$ was accepted as statistically significant.

Results

In the factor analysis of the symptom scores, three factors, psychomotor poverty, disorganization syndrome, and reality distortion, had Eigen values greater than unity and accounted for 77.3% of the variance in the symptom scores (Liddle and Barnes 1990). The rotated factor matrix is shown in Table 1.

TICV was found to be smaller in the schizophrenic patients than in the healthy subjects, although the difference was not statistically significant (schizophrenics vs controls, 1380 ± 87 vs 1416 ± 80 cm^3; t = 1.61, P = 0.11).

Table 2 shows the volume of HF in the two groups and the results of MANOVA. A significant effect of diagnosis was observed, but there were no significant effects of the side or of the diagnosis-by-side interaction. Schizophrenic patients showed a reduced volume of bilateral HFs (left mean difference 0.215 cm^3, P = 0.01; right mean difference 0.278 cm^3; P = 0.001). Significant negative correlations were observed between the volume of bilateral HF and the score for the disorganization syndrome (left, τ = –0.54, $P < 0.0001$; right, τ = –0.49, P = 0.0002). There were no significant correlations between the HF volume and the score for psychomotor poverty (left, τ = –0.20, P = 0.13; right, τ = –0.19, P = 0.14) or for reality distortion (left, τ = –0.24, P = 0.08; right, τ = –0.25, P = 0.06).

In the controls, the volume of the right HF significantly exceeded that of the left HF (mean difference 0.102 cm^3; t = 2.98, P = 0.006). However, in the schizophrenic patients, the difference in HF volume was small and not statistically significant (mean difference 0.039 cm^3; t =. 0.85, P = 0.40). Significant positive correlations were observed between the asymmetry index and the age at onset of illness (r = 0.46, P = 0.01; Fig. 1). However, there was no significant correlation between the asymmetry index and the duration of illness (r = –0.33, P = 0.09). There was no significant correlation between the scores of the

Table 2 Volume of hippocampal formation (values are mean ± SD; ranges are in parentheses). MANOVA multivariate analysis of variance

		Patients (n = 28)	Controls (n = 28)	MANOVA		
				Source	F-value	P-value
Volume (cm^3)	Left	2.797 ± 0.35 (2.191 – 3.667)	3.012 ± 0.21 (2.644 – 3.475)	Diagnosis	17.9	< 0.001
				Side	1.5	0.23
	Right	2.836 ± 0.40 (1.825 – 3.424)	3.114 ± 0.24 (2.664 – 3.555)	Diagnosis by side	0.3	0.59

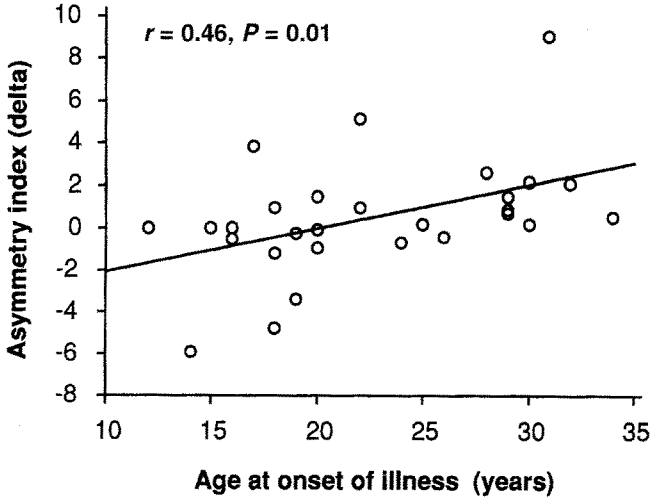

Fig. 1 Depiction of the correlation between the asymmetry index and age at onset of schizophrenia

three subsyndromes and the degree of asymmetry ($-0.22 < \tau < -0.10$, $0.11 < P < 0.48$).

Discussion

The present study confirmed the findings of Fukuzako et al. (1996) that the volume of the HF was reduced in schizophrenic patients as compared with that in healthy subjects. We also confirmed an association between the volume reduction of the HF and the disorganization syndrome. A new finding was that the significant asymmetry in the HF volume observed in the normal subjects was absent in the patients, although the degree of difference between the groups was insufficient to achieve a significant diagnosis-by-side interaction. Becker et al. (1990) demonstrated that the pattern of asymmetry in the HF was reversed compared with the patterns in the temporal lobe and parahippocampal gyrus in schizophrenic patients as well as in normal controls. However, all studies of MRI volumetry of the HF, except for that of Cook et al. (1992), showed the HF volume to be larger on the right side in normal controls (Jack et al. 1989; Adam et al. 1994; Soininnen et al. 1994; Gilmore et al. 1995; Jacobsen et al. 1996). The discrepancy between these findings and those of Becker et al. (1990) may be due to differences in study design.

Supporting the findings of Jacobsen et al. (1996), our present results revealed a significant positive correlation between the asymmetry index and the patient's age at the onset of schizophrenia. These findings suggest that a disturbance in normal hippocampal asymmetry may be associated with the earlier onset of illness, and may explain why our study showed no statistical significance between the HF volume asymmetry in schizophrenics and that in healthy subjects.

Increasing numbers of studies indicate that schizophrenia is of neurodevelopmental origin (Weinberger 1995). Although our results do not explain the etiology of the disturbed normal hippocampal asymmetry, they are consistent with those of other studies that demonstrate similar findings in other brain structures (Crow 1990; Falkai et al. 1992; Biler et al. 1994; Petty et al. 1995; Weinberger 1995). The hippocampus plays an important role in memory, particularly the spatial memory (Pribram 1986; Squire and Zola-Morgan 1991; Joseph 1992) and is involved in analyzing the context, forming the logical association and integrating emotion into mental activities (Berger et al. 1986; Gabriel et al. 1986; Olton et al. 1986; Eichenbaum et al. 1989). It has been suggested that some brain dysfunctions observed in schizophrenia may be linked to limbic structures in the medial temporal lobe (Torrey and Peterson 1974; Stevens 1986; Bogerts et al. 1991). We observed a significant correlation between the volume of the HF bilaterally and the score for the disorganization syndrome. We postulate that the disorganization syndrome may reflect a dysfunction of the anatomically interconnected limbic structures. However, no significant correlations were observed between the scores for clinical symptoms and the degree of asymmetry. Therefore, a disturbance in the morphologic asymmetry of the HF may not be related to specific clusters of clinical symptoms of schizophrenia.

In conclusion, we did not replicate findings of hippocampal asymmetry reported in the two previous studies (Becker et al. 1990; Jacobsen et al. 1996). However, our results support the finding of loss of normal hippocampal asymmetry reported by Jacobsen et al. (1996) when the age at onset of psychotic symptoms is considered.

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References

Adam C, Baulac M, Saint-Hilaire J-M, Laudau J, Granat O, Laplane D (1994) Value of magnetic resonance imaging-based measurements of hippocampal formations in patients with partial epilepsy. Arch Neurol 51:130–138

American Psychiatric Association (1987) Diagnostic and statistical manual of mental disorders (DSM-III-R), 3rd edn revised. American Psychiatric Press, Washington, DC

Andreasen NC (1984a) Scale for the Assessment of Negative Symptoms (SANS). University of Iowa, Iowa City

Andreasen NC (1984b) Scale for the Assessment of Positive Symptoms (SAPS). University of Iowa, Iowa City

Becker T, Elmer K, Mechela B, Schneider F, Taubert F, Schroth G, Grodd W, Bartels M, Beckmann H (1990) MRI findings in medial lobe structures in schizophrenia. Eur Neuropsychopharmacol 1:83–86

Berger TW, Berry SD, Thompson RF (1986) Role of the hippocampus in classical conditioning of aversive and appetitive behaviors. In: Isaacson RL, Pribram KH (eds) The hippocampus, vol 4. Plenum Press, New York, pp 203–240

Bilder RM, Wu H, Bogerts B, DeGreef G, Ashtari M, Alvir JMJ, Snyder PJ, Lieberman JA (1994) Absence of regional hemispheric volume asymmetries in first-episode schizophrenia. Am J Psychiatr 151:1437–1447

Bogerts B (1991) The neuropathology of schizophrenia: pathophysiological and neurodevelopmental implications. In: Mednic SA, Cannon TD, Barr CE (eds) Fetal neural development and adult schizophrenia. Cambridge University Press, Cambridge, pp 153–173

Chua SE, McKenna PJ (1995) Schizophrenia: a brain disease? A critical review of structural and functional cerebral abnormality in the disorder. Br J Psychiatry 166:563–582

Cook MJ, Fish DR, Shorvon SD, Straughan K, Stevens JM (1992) Hippocampal volumetric and morphometric studies in frontal and temporal lobe epilepsy. Brain 115:1001–1015

Crow TJ (1990) Temporal lobe asymmetries as the key to the etiology of schizophrenia. Schizophr Bull 16:433–443

Eichenbaum H, Wiener SI, Shapiro ML, Cohen NJ (1989) The organization of spatial coding in the hippocampus: a study of neural ensemble activity. J Neurosci 9:2764–2775

Falkai P, Bogerts B, Schneider T, Greve B, Pfeiffer U, Machus B, Fölsch-Reetz B, Majtenyi C, Ovary I (1992) Loss of sylvian fissure asymmetry in schizophrenia: a quantitative postmortem study. Schizophr Res 7:23–32

Fukuzako H, Fukuzako T, Hashiguchi T, Hokazono Y, Takeuchi K, Hirakawa 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

Gabriel M, Sparenborg S, Stolar N (1986) An executive function of the hippocampus: pathway selection for thalamic neuronal significance code. In: Isaacson RL, Pribram KH (eds) The hippocampus, vol 4. Plenum Press, New York, pp 1–40

Gilmore RL, Childress MD, Leonard C, Quisling R, Roper S, Eisenschenk S, Mahoney M (1995) Hippocampal volumetrics differentiate patients with temporal lobe epilepsy and extratemporal lobe epilepsy. Arch Neurol 52:819–824

Jack CR Jr, Twomey CK, Zinsmeister AR, Sharbrough FW, Petersen RC, Cascino GD (1989) Anterior temporal lobes and hippocampal formations: normative volumetric measurements from MR images in young adults. Radiology 172:549–554

Jacobsen LK, Giedd JN, Vaituzis AC, Hamburger SD, Rajapakse JC, Frazier JA, Kaysen D, Lenane MC, McKenna K, Gordon CT, Rapoport JL (1996) Temporal lobe morphology in childhood-onset schizophrenia. Am J Psychiatry 153:355–361

Joseph R (1992) The limbic system: emotion, laterality, and unconscious mind. Psychoanal Rev 79:405–456

Liddle PF, Barnes TRE (1990) Syndromes of chronic schizophrenia. Br J Psychiatry 157:558–561

Olton DS, Wible CG, Shapiro ML (1986) Mnemonic theories of hippocampal function. Behav Neurosci 100:852–857

Petty RG, Barta PE, Pearlson GD, McGilchrist IK, Lewis RW, Tien AY, Pulver A, Vaughn DD, Casanova MF, Powers RE (1995) Reversal of asymmetry of the planum temporale in schizophrenia. Am J Psychiatry 152:715–721

Pribram KH (1986) The hippocampal system and recombinant processing. In: Isaacson RL, Pribram KH (eds) The hippocampus, vol 4. Plenum Press, New York, pp 329–370

Schachter SC, Ransil BJ, Geschwind N (1987) Associations of handedness with hair color and learning disabilities. Neuropsychologia 25:269–276

Soininnen HS, Partanen K, Pitkanen A, Vainio P, Hanninen T, Hallikainen M, Koivisto K, Riekkinen PJ (1994) Volumetric MRI analysis of the amygdala and the hippocampus in subjects with age-associated memory impairment: correlation to visual and verbal memory. Neurology 44:1660–1668

Squire LR, Zola-Morgan S (1991) The medial temporal lobe memory system. Science 253:1380–1386

Stevens JR (1986) Clinicopathologic correlations in schizophrenia. Arch Gen Psychiatry 43:715–716

Torrey EF, Peterson MR (1974) Schizophrenia and the limbic system. Lancet II:942–946

Weinberger DR (1995) Neurodevelopmental perspectives on schizophrenia. In: Bloom FE, Kupfer DJ (eds) Psychopharmacology: the fourth generation of progress. Raven Press, New York, pp 1171–1183