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A Quantitative Magnetic Resonance Imaging Study of Patients with Schizophrenia

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Summary. Twenty patients with schizophrenia and ten normal control subjects underwent magnetic resonance imaging of the brain. The volumes of several brain structures were measured using a computer image analysing system. The schizophrenic patients had significantly smaller left parahippocampal volume and larger left temporal horn volume than the control subjects. A larger body of the right lateral ventricle could be estimated in the schizophrenics, but this difference was not significant. In the patient group a non-significant negative correlation was established between the presence of positive symptoms and the left temporal horn volume. There was no significant correlation between the temporal horn and temporal lobe or medial temporal structures. Our results indicate that the left medial temporal structure or left temporal lobe may be involved in schizophrenia and that temporal horn enlargement does not simply represent volume loss of the surrounding tissue.

Key words: Magentic resonance imaging – Schizophrenia – Ventricular enlargement – Temporal lobe

Introduction

Many findings from different studies have provided evidence of structural abnormalities in the schizophrenic brain. Among them, the presence of large cerebral ventricles on pneumoencephalograms (Haug 1982) and computed tomography (CT) scans (Johnstone et al. 1976) has been demonstrated conclusively. Studies of cortical sulcal enlargement in schizophrenia have also been reported (Weinberger et al. 1979; Shelton et al. 1988), but this finding has been less consistent than ventricular enlargement. These findings suggest that somewhere in the brain there has been either a loss of tissue or a failure of development. Two regions of the brain which have been widely investigated from a neuropathological viewpoint are the temporal lobe and the prefrontal lobe. Recent postmortem (Bogerts et al. 1985) and neuroimaging (DeLisi et al. 1988) brain studies have reported some morphological anomalies mainly in the medial temporal region. These structural imaging methods seem to be less sensitive in determining prefrontal pathology than other functional imaging studies such as regional cerebral blood flow (Weinberger et al. 1986) or glucose utilization (Buchsbaum et al. 1990).

Magnetic resonance imaging (MRI) makes it possible in living young subjects to determine brain pathology that has previously been observable only in neuroanatomical studies of postmortem brains. In comparison with CT, MRI provides finer spatial resolution and allows imaging in multiple planes. Moreover, a computer image analysing system provides several advantages for quantifying of structural brain volumes, including contrast enhancement, image magnification, and automated edge detection.

This article describes our initial experience with MRI volumetric study in schizophrenics and healthy controls. In this study, we measured several brain structures using a computer image analysing system to investigate the morphological changes in the schizophrenic brain, and examined the relationship between structural changes and clinical symptoms in the patients. In addition, we analysed whether any structural changes were correlated with each other.

Subjects and Methods

Twenty right-handed male patients were recruited from the inpatient and outpatient facilities of the Department of Neuropsychiatry, Kanazawa University Hospital. The mean age of the patients was 28.5, SD 5.5 (range 20–38) years, mean education level 14.3, SD 1.8 (range 11–16) years, mean height 171.3, SD 4.6 (range 162–178) cm, and mean weight 65.8, SD 11.0 (range 49–85) kg. The patients satisfied DSM-III-R (American Psychiatric Association 1987) criteria for schizophrenia ($n = 19$) or schizophreniform disorder ($n = 1$, who was diagnosed as having schizophrenia afterwards). The mean age at the time of their initial psycho-

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pathology was 21.8, SD 3.9 (range 15.3–29.5) years, and the mean duration of illness was 80.6, SD 58.9 (range 2–192) months. All the patients had received neuroleptic treatment. Their mean chlorpromazine equivalent dose was 783.9, SD 972.2 (range 33–3600) mg/day during the study. They had no history of electroconvulsive therapy prior to the study. No patient with a history of alcohol, other drug abuse, or neurological disease was included in the study.

The age-matched control group consisted of ten right-handed male volunteers, who ranged in age from 25 to 37 years with a mean age of 30.0, SD 4.2 years. Their mean educational level was more than 18 years, and all were graduates of a medical university. The mean height of the control subjects was 171.2, SD 4.7 (range 165–177) cm and the mean weight was 62.0, SD 4.7 (range 57–70) kg. None had a history of serious medical, neurological, or psychiatric illness. All the patients and volunteers gave informed consent to participate in this study.

MRI Scans

Brain images were acquired on a 1.5 T General Electric Sigma MRI scanner. A 28-cm crossed-ellipse head coil was used which provided high resolution images of the brain. An initial 3-mm sagittal series was used for slice orientation and midsagittal measurement, by identifying the anterior commissure-posterior commissure line. T1-weighted coronal slices through the temporal lobe structure were collected at an angle approximately vertical to the anterior-posterior commissure line [repetition time (TR), 500 ms; echo time (TE), 20 ms; effective slice thickness, 5 mm without separation; field of view (FOV), 20 cm]. Finally, T1-weighted axial slices were obtained through the entire brain, approximately parallel to the anterior commissure-posterior commissure line (TR, 500 ms; TE, 20 ms; effective slice thickness, 5 mm without separation; FOV, 20 cm).

Morphometric measurements were performed using an Avio Color Image Processor (SPICA-II, Nippon Avionics, Tokyo) that consists of a light box, a video camera, and an image processor within the computer. Areas so defined were summed across slices and multiplied by slice thickness to obtain structural volumes. All measurements were performed under blind conditions and cases were ordered randomly. The following regions of interest were quantified bilaterally.

Total hemispheric volume. Twenty-four consecutive coronal and axial sections were obtained. The total hemispheric volume was calculated by combining the coronal measurements (from the genu to the splenium of the corpus callosum) with the axial measurements (prefrontal portion and occipital portion) because the axial sections lacked a considerable area near the vertex, while the coronal sections lacked two adjacent areas to the frontal and occipital poles.

Prefrontal volume. In the axial slices, the prefrontal area was measured from the frontal pole to the manipulated boundary anterior to the genu of the corpus callosum.

Total temporal volume. The total temporal areas were measured in coronal sections from the anterior pole to the most caudal section anterior to a section in which the posterior horn of the lateral ventricle was visualized. In the caudal part of the temporal lobe, the medial boundary was defined by drawing a straight line from the medial tip of the lower limb of the sylvian fissure to the lateral tip of either the hippocampal or entorhinal fissure.

Limbic structural volume. The posterior extension of the amygdala and the anterior parts of the hippocampus could not be demarcated reliably. Among all sections that made up the total temporal volume, two consecutive sections in which the amygdala appeared obviously were measured as the amygdala volume, and subsequent caudal sections were also measured as the hippocampal volume. The parahippocampal gyrus was measured in all sections that made up the amygdala and hippocampal volume. The amygdala volume consisted of a grey matter region, with the temporal horn or white matter as the medial, inferior and lateral boundary, and the cortical surface as the superior boundary. The medial portion of the amygdala was demarcated by the white matter from the uncal cortex that was included in the parahippocampal volume. The hippocampal volume included the dentate gyrus and the subiculum. The boundary between the subiculum and the parahippocampal gyrus was defined as the most medial portion of the subiculum-parahippocampal gyrus junction. The parahippocampal volume consisted of the gyral and sulcal components of the parahippocampal grey matter.

Lateral or third ventricle volume. The lateral ventricle and the third ventricle volumes were measured in each coronal section in which they appeared. Then we divided this lateral ventricle volume into four anatomical parts (i.e. the anterior horn, body, posterior horn and temporal horn). The most caudal section of the anterior horn showed the interventricular foramen. The most rostral section of the posterior horn was an adjacent section posterior to the genu of the corpus callosum, which contained the junction of the ventricle from the body to the temporal horn.

Corpus callosum area. The midsagittal slices that gave the clearest outline of the corpus callosum were used for measurement.

To assess the reliability of the MRI measurements, prefrontal and temporal regions of ten brains were measured by a second rater (inter-rater reliability) and again by the first rater (test-retest reliability). The average interclass correlation values for inter-rater and test-retest reliability were 0.792 and 0.804 respectively.

Clinical symptoms were assessed by two psychiatrists using the Positive and Negative Syndrome Scale (PANSS) of Kay and Opler (1991) within 2 weeks of the MRI study, with each mean score adopted.

Statistical Analysis

The Mann-Whitney U test was applied between the patient and control groups. Kendall's rank correlation coefficient was used between MRI variables and general characteristics or clinical symptoms, and among the MRI variables. Bonferroni adjustment of alpha-error required $P < 0.00227$ (0.05:22 regions) as the level of statistical significance. We adjusted the criterion of significance to $P < 0.0025$ and that indicating trends to $P < 0.005$.

Results

Comparison of Schizophrenics and Controls

As shown in Table 1, the schizophrenic patients had a significantly smaller left parahippocampal volume ($P = 0.0016$) and larger left temporal horn ($P = 0.0001$) on MRI than the control subjects. Furthermore, a larger body of the right lateral ventricle ($P = 0.0042$) could be estimated in the patients, but this difference was not significant.

Correlation Between MRI Variables and General Characteristics or Clinical Symptoms

In both the patient and control groups, no MRI variable correlated with age, education level, height, body weight, age at the onset of illness, duration of illness, or chlorpromazine equivalent dose. In the patient group, a non-significant negative correlation coefficient was obtained between the positive symptom score on PANSS and the

Table 1. Comparison of MRI measurements in schizophrenics and controls

Regions	Schizophrenics Mean (SD)	Controls Mean (SD)
Total hemispheric volume (cm^3)		
Left side	486.5 (37.8)	510.3 (34.1)
Right side	496.4 (41.8)	519.2 (40.3)
Prefrontal volume (cm^3)		
Left side	57.9 (7.1)	68.0 (10.0)
Right side	62.4 (8.9)	69.1 (9.7)
Total temporal volume (cm^3)		
Left side	61.8 (5.8)	62.9 (7.2)
Right side	64.2 (6.9)	64.6 (8.0)
Limbic structural volume		
Amygdala volume (cm^3)		
Left side	1.66 (0.23)	1.90 (0.22)
Right side	1.81 (0.25)	2.02 (0.18)
Hippocampal volume (cm^3)		
Left side	2.02 (0.30)	1.94 (0.27)
Right side	2.17 (0.44)	2.05 (0.45)
Parahippocampal volume (cm^3)		
Left side	1.72 (0.21)**	1.97 (0.15)
Right side	1.83 (0.30)	1.96 (0.26)
Lateral ventricle volume		
Anterior horn (cm^3)		
Left side	3.38 (1.03)	2.84 (1.13)
Right side	3.15 (1.18)	2.58 (0.87)
Body (cm^3)		
Left side	3.03 (0.96)	2.04 (1.03)
Right side	2.79 (0.96)*	1.65 (0.77)
Posterior horn (cm^3)		
Left side	3.07 (1.17)	2.50 (0.80)
Right side	2.70 (1.13)	1.98 (1.09)
Temporal horn (cm^3)		
Left side	0.55 (0.27)**	0.20 (0.10)
Right side	0.60 (0.25)	0.43 (0.23)
Third ventricle volume (cm^3)	1.51 (0.50)	1.21 (0.30)
Corpus callosum area (cm^2)	6.02 (0.73)	6.07 (0.41)

SD, Standard deviation
* $P < 0.005$; ** $P < 0.0025$ compared with controls by Mann-Whitney U test

left temporal horn volume ($t = -0.467$, $P = 0.004$). To estimate the relationship between the temporal horn and surrounding structures in the schizophrenic brain, we calculated the correlation coefficients between temporal horn volume and the volumes of the amygdala, hippocampus, parahippocampus and total temporal lobe. None of these coefficients was statistically significant.

Discussion

Our volumetric study using MRI demonstrated a decreased left parahippocampal volume in patients with schizophrenia. This finding is in agreement with recent neuropathological postmortem studies (Jakob and Beckmann 1986; Falkai et al. 1988; Altshuler et al. 1990) which have emphasized medial temporal structures as the sites of the principal abnormalities in schizophrenia. Recent MRI studies have reported morphological changes in the amygdala (Barta et al. 1990) or hippocampus (Bogerts et al. 1990). More recently, Shenton et al. (1992) reported a more precise MRI volumetric study. In their study there was a lateralized (left-sided) decrease in the volume of the anterior hippocampus-amygdala and parahippocampal gyrus. Our data replicated their findings in the left parahippocampal gyrus, however, our study did not confirm morphological changes in the amygdala ($P = 0.01$ on the left side, statistically insignificant) or hippocampus.

Our study also demonstrated that the left temporal horn was significantly enlarged and that the right body of the lateral ventricle showed a statistically insignificant trend to increased volume in schizophrenia. Previous CT and MRI studies have established that increased ventricular size is the most prevalent finding in the schizophrenic brain (Andreasen et al. 1990; Daniel et al. 1991). Crow et al. (1989) considered asymmetrical enlargement of the left temporal horn to be important in the pathogenesis of schizophrenia. The most statistically significant finding of our study is left temporal horn enlargement in the patient group. Although our statistical design could not directly deal with asymmetrical differences between the patients and controls, our findings indicate discrete pathology in the left medial temporal structures.

Pakkenberg et al. (1987) reported hemispheric volume reduction in schizophrenic postmortem brain, whereas Heckers et al. (1991) found no significant volume changes of hemisphere in schizophrenics. In our study no statistically significant difference was found between patient and control groups in either hemisphere. Owing to our methodological limitation in the MRI system, we calculated the total hemispheric volume by combing the coronal images with the axial images. Therefore, there is the possibility that our less precise assessment overlooked subtle abnormality of the total hemispheric volume.

Smaller frontal lobes (Andreasen et al. 1986) and smaller left frontal lobe (De Myer et al. 1988) could not be confirmed in this study ($P = 0.012$ on the left side, statistically insignificant). As in our prefrontal measurement, except for coronal measurement, Suddath et al. (1989) also failed to demonstrate a smaller prefrontal volume. The assessment of the prefrontal volumes is likely to be highly variable, if the maniplated boundary is defined as anterior to the genu of the corpus callosum. Normal right-handed subjects, for instance, have anatomical asymmetry with the left prefrontal length shorter than the right prefrontal length, whereas schizophrenic patients have inverse asymmetry in the prefrontal region (Luchins et al. 1979). It is conceivable that this inverse asymmetry could overshadow subtle volumetric changes. It is possible that further refinements in measurement will demonstrate these subtle changes.

The finding of an association between structural changes and schizophrenic symptoms remains preliminary but is gaining support. Associations between fron-

tal lobe atrophy and negative symptoms (Uematsu and Kaiya 1989; Andreasen et al. 1990) and between temporal lobe atrophy and positive symptoms (Barta et al. 1990) have been reported. Negative symptoms were not correlated with any MRI variables in this study. In our study, however, there was a statistically insignificant trend indicating that patients with a larger left temporal horn volume show less severe positive symptoms as assessed by the PANSS. The failure to detect strong associations between clinical symptoms and cerebral abnormalities may reflect some difficulty in evaluating clinical symptoms. For example, by means of the PANSS, Kay et al. (1986) suggested that the good prognosis conveyed by an early negative profile seems to reverse in the chronic phase, at which point a negative syndrome carries the expected ominous implications. Pharmacological studies have also indicated that the difference in the distribution of the antipsychotic response in schizophrenics suggests at least two populations (i.e. neuroleptic responders and non-responders; Smith et al. 1979; Garver et al. 1984). For example, some schizophrenic patients with substantially higher doses of medication have not stopped hallucinating or experiencing delusions which are generally improved by neuroleptic treatment. Further studies about the role of brain structure in producing clinical symptoms should take into account these clinical heterogeneities.

Suddath et al. (1989) presented evidence for a reduced volume of the temporal lobe, which was inversely correlated with the area of the temporal horn. Shenton et al. (1992) also reported that the volume of the temporal horn correlated negatively with that of the left parahippocampal gyrus. Bogerts et al. (1990), however, did not replicate this correlation and suggested that the lack of this correlation is consistent with a developmental disturbance or hypoplasia rather than with progressive degenerative tissue loss. In our study, in accordance with Bogerts et al., there was no significant correlation between the left temporal horn and temporal lobe or medial temporal structures. The possibility exists that the volumetric study makes these relationships more intricate as a result of continuous shape changes among the slices. We further calculated Kendall's tau between the temporal horn area and the area of the temporal lobe or limbic structural areas (i.e. amygdala, hippocampus, or parahippocampus) on two different slices each where the amygdala or the hippocampal formation respectively was most visible. There was also no significant correlation among these variables. Our results indicate that temporal horn enlargement does not simply represent volume loss of the surrounding tissue. Even if volumetric tissue changes are present in the schizophrenic brain, shape deviation should be considered when interpretating ventricular enlargement. Moreover, the asymmetrical pattern of normal human brain development (Chi et al. 1977) would provide an explanation for the structural changes seen in the brains of schizophrenics.

Medial temporal structures have been shown to be involved in supramodal sensory integration and association at the highest neuronal level. Some physiological investigations as well as our SPECT study (Kawasaki et al. 1992) reported increased function in the temporal lobe (DeLisi et al. 1989) or medial temporal structure (Musalek et al. 1989). There is an intriguing relationship, suggesting that reduced volumes of the medial temporal structures reveal increased functional activity. This relationship is quite different from the neurodegenerative process in which reduced volume of brain structures reflects decreased functional activity (Pearlson et al. 1992). The precise relationship between these anatomical findings, functional changes and clinical symptoms should be elucidated by further studies.

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References

Altshuler LL, Casanova MF, Goldberg TE, Kleinman JE (1990) The hippocampus and parahippocampus in schizophrenic, suicide, and control brains. Arch Gen Psychiatry 47:1029–1034

American Psychiatric Association, Committee on Nomencalture and Statistics (1987) Diagnostic and statistical manual of mental disorders, 3rd edn, revised American Psychiatric Association, Washington, D.C.

Andreasen NC, Nasrallah HA, Dunn V, Olson SC, Grove WM, Ehrhardt JC, Coffman JA, Crossett JHW (1986) Structural abnormalities in the frontal system in schizophrenia: a magnetic resonance imaging study. Arch Gen Psychiatry 43:136–144

Andreasen NC, Ehrhardt JC, Swayze VW, Alliger RJ, Yuh WTC, Cohen G, Ziebell S (1990) Magnetic resonance imaging of the brain in schizophrenia: the pathophysiologic significance of structural abnormalities. Arch Gen Psychiatry 47:35–44

Barta PE, Pearlson GD, Powers RE, Richards SS, Tune LE (1990) Auditory hallucinations and smaller superior temporal gyral volume in schizophrenia. Am J Psychiatry 147:1457–1462

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

Bogerts B, Ashtari M, Degreef G, Alvir JMJ, Bilder RM, Lieberman JA (1990) Reduced temporal limbic structure volumes on magnetic resonance images in first episode schizophrenia. Psychiatry Res Neuroimaging 35:1–13

Buchsbaum MS, Nuechterlein KH, Haier RJ, Wu J, Sicotte N, Hazlett E, Asarnow R, Potkin S, Guich S (1990) Glucose metabolic rate in normals and schizophrenics during the continuous performance test assessed by positron emission tomography. Br J Psychiatry 156:216–227

Chi JG, Dooling EC, Gilles FH (1977) Gyral development of the human brain. Ann Neurol 1:86–93

Crow TJ, Ball J, Bloom SR, Brown R, Bruton CJ, Colter N, Frith CD, Johnstone EC, Owens DGC, Roberts GW (1989) Schizophrenia as an anomaly of development of cerebral asymmetry. Arch Gen Psychiatry 46:1145–1150

Daniel DG, Goldberg TE, Gibbons RD, Weinberger DR (1991) Lack of a bimodal distribution of ventricular size in schizophrenia: a gaussian mixture analysis of 1056 cases and controls. Biol Psychiatry 30:887–903

DeLisi LE, Dauphinais D, Gershon ES (1988) Perinatal complications and reduced size of brain limbic structures in familial schizophrenia. Schizophr Bull 14:185–191

DeLisi LE, Buchsbaum MS, Holcomb HH, Langston KC, King AC, Kessler R, Picker D, Carpenter WT, Morihisa JM, Margolin R, Weinberger DR (1989) Increased temporal lobe glucose use in chronic schizophrenic patients. Biol Psychiatry 25:835–851

De Myer MK, Gilmer RL, Hendrie HC, De Myer WE, Augustyn GT, Jackson RK (1988) Magnetic resonance brain images in

schizophrenic and normal subjects: influence of diagnosis and education. Schizophr Bull 14:21–37
Falkai P, Bogerts B, Rozumek M (1988) Cell loss and volume reduction in the entorhinal cortex of schizophrenics. Biol Psychiatry 24:515–521
Garver CL, Zemlan F, Hirschowitz J, Hitemann R, Mavroidis ML (1984) Dopamine and non-dopamine psychoses. Psychopharmacology 84:138–140
Haug JO (1982) Pneumoencephalographic evidence of brain atrophy in acute and chronic schizophrenic patients. Acta Psychiatr Scand 66:374–383
Heckers S, Heinsen H, Heinsen Y, Beckmann H (1991) Cortex, white matter, and basal ganglia in schizophrenia: a volumetric postmortem study. Biol Psychiatry 29:556–566
Jakob H, Beckmann H (1986) Prenatal developmental disturbances in the limbic allocortex of schizophrenics. J Ment Transm 65:303–326
Johnstone EC, Crow TJ, Frith CD, Husband J, Kreel L (1976) Cerebral ventricular size and cognitive impairment in chronic schizophrenia. Lancet II:924–926
Kawasaki Y, Suzuki M, Maeda Y, Urata K, Yamaguchi N, Matsuda H, Hisada K, Suzuki M, TakashimaT (1992) Regional cerebral blood flow in patients with schizophrenia: a preliminary report. Eur Arch Psychiatry Clin Neurosci 241:195–200
Kay SR, Fiszbein A, Lindenmyer JP, Opler LA (1986) Positive and negative syndromes in schizophrenia as a function of chronicity. Acta Psychiatr Scand 74:507–518
Kay SR, Opler LA, Fiszbein A (1991) Positive and negative syndrome scale (PANSS) rating manual. Multi-Health Inc, Ontario
Luchins DJ, Weinberger DR, Wyatt RJ (1979) Schizophrenia: evidence of a subgroup with reversed cerebral asymmetry. Arch Gen Psychiatry 36:1309–1311
Musalek M, Podreka I, Walter H, Suess E, Passweg V, Nutzinger D, Strobl R, Lesch OM (1989) Regional brain function in hallucinations: a study of regional cerebral blood flow with 99m-Tc-HMPAO-SPECT in patients with auditory hallucinations, tactile hallucinations, and normal controls. Compr Psychiatry 30:99–108
Pakkenberg B (1987) Post-mortem study of chronic schizophrenic brains. Br J Psychiatry 151:744–752
Pearlson GD, Harris GJ, Powers RE, Barta PE, Camargo EE, Chase GA, Noga JT, Tune LT (1992) Quantitative changes in mesial temporal volume, regional cerebral blood flow, and cognition in Alzheimer's disease. Arch Gen Psychiatry 49:402–408
Shelton RC, Karson CN, Doran AR, Pickar D, Bigelow LB, Weinberger DR (1988) Cerebral structural pathology in schizophrenia: evidence for a selective prefrontal cortical defect. Am J Psychiatry 145:154–163
Shenton M, Kikinis R, Jolesz FA, Pollak AD, LeMay M, Wible CG, Hokama H, Martin J, Metcalf D, Coleman M, McCarley RW (1992) Abnormalities of the left temporal lobe and thought disorder in schizophrenia: a quantitative magnetic resonance imaging study. N Engl J Med 327:604–612
Smith RC, Crayton J, Dekirmenjian H, Klass D, Davis JM (1979) Blood levels of neuroleptic drugs in non-responding chronic schizophrenic patients. Arch Gen Psychiatry 36:579–584
Suddath RL, Casanova MF, Goldberg TE, Daniel DG, Kelsoe JR, Weinberger DR (1989) Temporal lobe pathology in schizophrenia: a quantitative magnetic resonance imaging study. Am J Psychiatry 146:464–472
Uematsu M, Kaiya H (1989) Midsagittal cortical pathomorphology of schizophrenia: a magnetic resonance imaging study. Psychiatry Res 30:11–20
Weinberger DR, Torrey EF, Neophytides AN, Wyatt RJ (1979) Structural abnormalities of the cerebral cortex of chronic schizophrenic patients. Arch Gen Psychiatry 36:935–939
Weinberger DR, Berman KF, Zec RF (1986) Physiologic dysfunction of dorsolateral prefrontal cortex in schizophrenia: I. regional cerebral blood flow evidence. Arch Gen Psychiatry 43:114–124