Eur Arch Psychiatry Clin Neurosci (2000) 250 : 169–174

ORIGINAL PAPER

Toshiki Shioiri · Hiroshi Hamakawa · Tadafumi Kato · Kumiko Fujii · Jun Murashita
Toshiro Inubushi · Toshiyuki Someya

Frontal lobe membrane phospholipid metabolism and ventricle to brain ratio in schizophrenia: preliminary ^{31}P-MRS and CT studies

Received: 26 April 1999 / Accepted: 22 February 2000

Abstract A number of studies employing in vivo phosphorous-31 magnetic resonance spectroscopy (^{31}P-MRS) have demonstrated alterated measurements of frontal phospholipid and high energy phosphorus metabolism in schizophrenia. Enlargement of both the cerebroventricular system and the cortical sulci also has been reported as the most consistent pathological finding in schizophrenia by several investigators. To our knowledge, however, only two studies have simultaneously examined structural and functional aspects of the biological substrate of schizophrenia in the same patients. Moreover, they may have failed to find a significant correlation between these variables because of small sample sizes. The possible relationship between frontal lobe membrane phospholipid metabolism and ventricle-to-brain ratio (VBR) in patients with schizophrenia was investigated. In 31 schizophrenic patients, frontal lobe membrane phospholipid metabolism was measured by ^{31}P-MRS, and VBR was measured by computed tomography (CT). Stepwise multiple regression analysis disclosed that VBR positively correlated only with increased phosphodiester (PDE) level (β = 0.381, p = 0.0345), but with no other metabolites. This finding may provide evidence for an association between structural brain abnormality and altered frontal lobe membrane metabolism in schizophrenic patients, although the p-value of the finding is not high.

T. Shioiri, M. D., Ph. D. (✉) · T. Someya
Dept. of Psychiatry
Niigata Univ. School of Medicine
1–757 Asahimachi, Niigata 951–8510, Japan
E-mail:tshioiri@med.niigata-u.ac.jp

H. Hamakawa · K. Fujii · J. Murashita
Department of Psychiatry, Shiga University of Medical Science, Otsu, Shiga, Japan

T. Kato
Department of Neuropsychiatry, Faculty of Medicine, University of Tokyo, Tokyo, Japan

T. Inubushi
Molecular Neurobiology Research Center, Shiga University of Medical Science, Otsu, Shiga, Japan

Key words Phosphorous–31 magnetic resonance spectroscopy (^{31}P-MRS) · Frontal lobe · Ventricle-to-brain ratio (VBR) · Phosphomonoester (PME) · Phosphodiester (PDE)

Introduction

Structural brain abnormalities in schizophrenia include ventricular enlargement, significant non-localized loss of cortical gray matter, loss of the normal cerebral asymmetries, asymmetric reduction in limbic and temporal cortical structures and also bilateral loss (see DeLisi et al. 1997). Among all these findings, the most consistent pathological finding in schizophrenia is enlargement of both the cerebroventricular system and the cortical sulci, an expansion that cannot be accounted for by common causes of cerebral atrophy, such as alcoholism, drug abuse or aging (Nair et al. 1997). The ventricular-to-brain ratio (VBR) is the most frequently studied anatomic variable (Mozley et al. 1994), and a recent review of investigations measuring VBR in schizophrenics showed that ventricular size in schizophrenics was larger than in controls (see McCarley et al. 1999).

Phosphorus MRS (^{31}P-MRS) is a non-invasive investigational tool that can provide in vivo information about membrane phospholipid and high-energy phosphate metabolism in the brain (Cady 1990), supplying information on the metabolic brain abnormalities in schizophrenia. In recent years, a number of ^{31}P-MRS studies have found lower levels of phosphomonoester (PME) in schizophrenic patients (Pettegrew et al. 1991; Williamson et al. 1991; Stanley et al. 1994; Fukuzako et al. 1999a; Potwarka et al. 1999; Volz et al. 1999), including the precursors necessary for the synthesis of membrane phospholipids (Dawson 1985), except for in a few studies (Volz et al. 1997, 1998). Many studies have also found higher levels of phosphodiesters (PDE) in schizophrenics (Pettegrew et al. 1991; Deicken et al. 1994; Stanley et al. 1994; Fukuzako et al. 1999a, 1999b), although there are a few reports with contrary results (Williamson et al. 1991; Fujimoto et

al. 1992). PDE are found in the catabolic pathway in membrane phospholipid metabolism (Dawson 1985). We also noted these abnormalities in our study conducted with ^{31}P-MRS in the frontal region of schizophrenic patients (Shioiri et al. 1994, 1997; Kato et al. 1995).

In addition to schizophrenia, decreased PME and/or increased PDE, on the other hand, have been associated with chronic cerebral infarction (Sappey-Marinier et al. 1992), severe demyelinating disorders (van der Knaap et al. 1992), and anorexia nervosa (Kato et al. 1997). It should be noted that most of these disorders, including schizophrenia, in which reductions of PME have been reported are also characterized to varying degrees by brain atrophy. The reported abnormalities of PME and/or PDE could reflect decreased membrane phospholipid metabolism, and this metabolic change could be related to brain atrophy in these disorders. However, only a few studies have simultaneously examined structural and functional aspects of the biological substrate of schizophrenia in the same patients (Keshavan et al. 1993; Hinsberger et al. 1997). Keshavan et al. (1993) and Hinsberger et al. (1997) may have failed to find a significant correlation between these variables because they used a small sample sizes (n = 9 and 10, respectively).

In this study, we hypothesized that abnormal frontal lobe metabolism in schizophrenia may be related to measurements of altered cerebral morphology, in particular, ventricular size. In other words, decreased PME and/or increased PDE might be correlated with ventricular enlargement in schizophrenia. Therefore, we measured VBR on CT scans of 31 schizophrenic patients, and we also measured frontal lobe membrane phospholipids and high-energy phosphate metabolism using ^{31}P-MRS.

Subjects and methods

Thirty-one schizophrenic patients (19 men and 12 women) who ranged in age from 15 to 47 years (mean age = 28.7 years, SD = 10.1 years) participated in this study (Table 1). All were hospitalized at Shiga University of Medical Science Hospital. The patients were evaluated in two interview sessions of one hour each conducted by two senior psychiatrists, who consensually made diagnoses according to the DSM-IV criteria (American Psychiatric Association 1994). Subtype diagnoses are presented in Table 1. The mean duration of illness was 6.0 years (SD = 7.1 years). No patients had a history of head injury, neurologic disorders, drug or alcohol abuse, or serious medical illnesses.

Eight of the schizophrenic patients had been free of neuroleptic medications for at least two weeks prior to the study. The remaining 23 patients were being treated with neuroleptics at dosages in chlorpromazine equivalents (Gelenberg 1983) ranging from 169 to 2150 mg per day (mean dosage = 610 ± 606 mg/day). Nine patients were also treated with benzodiazepines as sleep inducers. None of the patients was taking any medication other than the neuroleptics and/or benzodiazepines. Informed consent was obtained from all subjects.

VBR methods

Before ^{31}P-MRS was performed, all patients underwent computed tomography (CT). Patients who had structural brain abnormalities (e. g., trauma, infarction, bleeding, and neoplasma) other than ventricular enlargement, as determined by experienced neuroradiologists who were unaware of the design of this study, were excluded. The CT scans were obtained using a Somatom DR scanner (Siemens, Forchheim, Germany) depicting 12 slices (8.1 mm thick) through the brain, parallel to and starting 10 mm above the orbotomeatal plane. Scanning variables were kept constant. Using Adobe Photoshop 3.0J on a Macintosh personal computer, all slices were enlarged to approximately the same size as the actual head. From the axial slices, we chose the three consecutive slices visually judged to show the largest lateral ventricular area. Using the above-mentioned imaging software, visible internal cerebrospinal fluid (CSF) space was delineated manually and the area automatically computed by planimetry. The area of the brain was calculated similarly from the same slice. In the three slices, these area measurements were repeated several times by one neuropsychiatrist (H. H.) who was unaware of the diagnosis of the patients, and average intermeasurement CVs were less than 1 %. The average of the measurements was used in calculating the VBR (ventricular-brain ratio), and among the three VBRs, we adopted the highest VBR as the VBR of the subject, as described in previous studies (Andreasen et al. 1982; Pearlson et al. 1989; Wurthmann et al. 1995). Thus, the VBR was defined as the area of the lateral ventricles at their largest extent as a percentage of the entire brain area at that level.

^{31}P-MRS methods

The method of MRS data acquisition and its reliability were described in previous reports (Shioiri et al. 1996, 1997). In brief, subjects were examined on a 1.5T SIGNA MR system (GE Medical Systems, Wisconsin, USA) equipped with a spectroscopy package. Surface coils for ^{1}H and ^{31}P (GE Medical Systems) were placed over the subject's head. The volume of interest was the 30 mm slice between the front pole and the front edge of the corpus callosum parallel to the coil. ^{31}P-MR spectra were obtained using depth-resolved surface coil spectroscopy (DRESS) (Bottomley et al. 1984). The repetition time (TR) was set at 3 s. One hundred twenty-eight scans were averaged.

The data sets obtained were numbered and then randomly ordered for processing by a single person who was blinded to the diagnosis and clinical status of the subjects. Free induction decays (FID) were processed using a SPARC II workstation (Sun Microsystems, California, USA) with OMEGA software (GE). Broad peaks and baseline distortion were canceled using the convolution difference method (Campbell et al. 1973). Fifteen hertz line-broadening, Fourier transformation, automatic first-order phase correction, and manual zero-order phase correction were applied. Additionally, baseline correction with linear tilt was applied to the phase-corrected spectra after manual definition of five points known to have no signal. Next, the following seven peaks were resolved: phosphomonoester (PME), inorganic phosphate (Pi), phosphodiester (PDE), creatine phosphate (PCr), and three resonances from adenosine triphosphate (ATP), i. e., γ, α, and β-ATP (Cady 1990).

The peak areas were calculated by automatic peak fitting with Lorenzian curves by the SIMPLEX method using a software package that was programmed in our laboratory for use with an IBM personal computer. The peak areas are expressed as the percent values of the total phosphorous signal (peak area %).

Statistical analysis

In order to analyze the relationships between the VBR and the seven brain phosphorus metabolites in all 31 schizophrenic subjects, we performed Pearson's correlation coefficient and stepwise multiple regression analysis with seven phosphorus metabolites as the independent variables. These statistical analyses were carried out using SPSS programs. Data were expressed as mean ± S. D. A probability level of less than 0.05 was regarded as statistically significant.

This study had been approved by the ERB of Shiga University of Medical Science.

Table 1 Demographic and clinical characteristics of schizophrenic patients

Patient	Sex	Age (years)	Education (years)	Diagnosis (DSM-III-R)	Years of illness	Dose (mg/day)
1	F	15	9	Undifferentiated	1	338
2	F	15	9	Undifferentiated	1	750
3	F	18	12	Undifferentiated	0	0
4	F	20	12	Paranoid	3	1575
5	F	23	14	Paranoid	0	450
6	F	32	12	Undifferentiated	12	225
7	F	32	14	Undifferentiated	2	300
8	F	37	9	Paranoid	17	0
9	F	37	12	Disorganized	7	500
10	F	45	16	Disorganized	4	675
11	F	47	15	Undifferentiated	29	450
12	F	52	9	Paranoid	12	1500
13	M	18	12	Undifferentiated	1	1200
14	M	19	12	Undifferentiated	4	750
15	M	19	12	Catatonic	0	2150
16	M	20	12	Catatonic	1	800
17	M	20	12	Disorganized	2	1500
18	M	21	12	Undifferentiated	2	0
19	M	21	18	Undifferentiated	2	0
20	M	23	9	Catatonic	2	1500
21	M	26	16	Paranoid	7	317
22	M	26	11	Disorganized	9	1125
23	M	27	9	Paranoid	0	0
24	M	28	12	Disorganized	4	450
25	M	29	12	Undifferentiated	6	200
26	M	30	16	Paranoid	4	0
27	M	31	9	Paranoid	0	169
28	M	36	16	Residual	13	0
29	M	37	9	Disorganized	12	1500
30	M	40	6	Undifferentiated	6	0
31	M	45	16	Disorganized	24	500
Total(mean ± SD)		28.7 ± 10.1	12.1 ± 2.8		6.0 ± 7.1	610 ± 606

Note: Neuroleptic dosages are given in chlorpromazine equivalents (Gelenberg, 1983).
Diagnostic subtypes were based on DSM-III-R criteria (APA, 1987). *Values are mean ± SD.

Results

Figure 1 shows a significant relationship between the VBR and the level of PDE in the schizophrenic frontal lobe ($r = 0.39$, $p = 0.0325$) although there was no significance after Bonferoni correction. We also found a tendency for the level of PME, which is another membrane phospholipid, to be inversely correlated with the VBR ($r = -0.263$, $p = 0.15$). To confirm these relationships, stepwise multiple regression analysis was performed, revealing that the VBR positively correlated with only increased PDE level, but with no other metabolites (for PDE: multiple R=0.381, $\Delta R^2 = 0.145$, $\beta = 0.381$, $F = 4.92$, $p = 0.0345$). No VBRs and seven phosphorous metabolites were significantly correlated with present age, age at onset, duration of illness, dosage of neuroleptics, diagnostic subtypes, and education.

Discussion

In the present study, we found a significant but weak positive relationship between the VBR and the level of PDE in the frontal lobe of 31 schizophrenic patients. Additionally, we also found a trend for PME, which includes precursors necessary for the synthesis of membrane phospholipids (Dawson 1985). It is possible that this finding suggests an association between structural brain abnormality and altered frontal lobe membrane metabolism in schizophrenic patients, although there are some limitations of the present study as mentioned later. To our knowledge, however, this is the first report of such findings, although Keshavan et al. (1993) has reported a trend of ventricular size being positively correlated with PDE level in the frontal lobe of schizophrenic patients ($p = 0.15$). Therefore, we must interpret this finding very carefully.

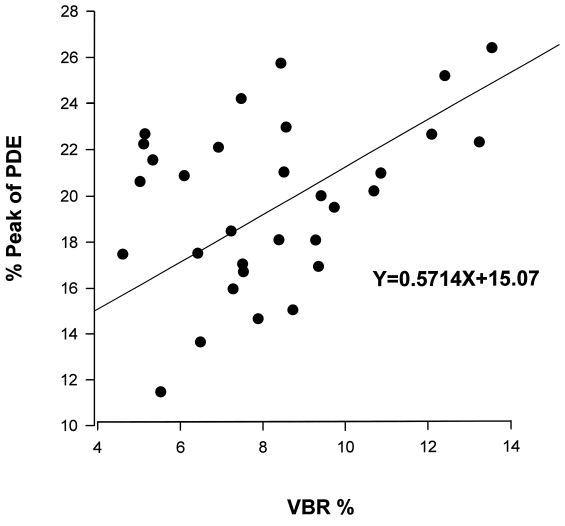

Fig. 1 Relationship between the VBR and PDE level in the frontal lobe of schizophrenics. The ordinate and abscissa indicate the level of PDE peak percent and the VBR (percentage of ventricle area/brain area). Each dot represents an individual subject. The solid line is the regression line. The coefficient of correlation is significant ($r = 0.39$, $p=0.0325$).

PDE is a product of phospholipase A1 and A2 activity and is converted to PME by PDE phosphodiesterase activity (Pettegrew et al. 1991). Decreased PDE phosphodiesterase activity could account for both the decreased PME level and increased PDE level observed in the schizophrenic patients with high VBR measurements. Thus, brain atrophy may reflect membrane phospholipid metabolism of neural cells in the brain, or at least in the frontal lobe in schizophrenia, particularly PDE phosphodiesterase activity, or alternatively, the change in membrane phospholipid metabolism (or PDE phosphodiesterase activity) may lead to brain atrophy. Keshavan et al. (1993) also suggested that altered membrane metabolism in the frontal lobe of schizophrenics may be associated with nonspecific cerebral atrophy. However, it is also possible that neuroleptics may influence PME and PDE results via possible alterations of phosphodiesterase and/or phospholipase A^1/A^2 activity, since two more recent studies showed changes in levels of phosphorus metabolites during neuroleptic treatments for schizophrenia (Fukuzako et al. 1999b; Volz et al. 1999).

On the other hand, there may be another explanation for the present findings. As mentioned above in the introduction, ventricular enlargement is one of the most consistent and common structural abnormalities in the schizophrenic brain (APA 1994; Nair et al. 1997). In addition, numerous published reports have already established reduced gray matter volume in schizophrenia (e. g., Zipursky et al. 1992; Ron et al. 1992; Schlaepfer et al. 1994; Lim et al. 1996a, 1996b). More recently, McCarley et al. (1999) reviewed more than 170 MRI anatomic studies of schizophrenia and described that 86 % of previous studies differentiating gray from white matter found evidence for localization of gray matter volume reduction. Therefore, it is also possible that the ventricular enlargement in schizophrenia may be related to gray matter loss. Moreover, PDE is more concentrated in the white than in the gray matter (Kilby et al. 1990). Therefore, we suggest the hypothesis that the decreased ratio of gray-to-white matter volume, due to atrophy and/or dysgenesis of the brain, may increase the PDE level in the frontal lobe of schizophrenic patients. However, Buchli et al. (1994) reported an increase in both PME and PDE in white matter compared to gray matter in ten normal subjects, although there are some differences in the method and subjects between their studies and ours. Moreover, it is difficult to interpret the results because, in this study, we examined the relationship between VBR, a measure of diffuse cerebral atrophy (based on CSF space), with a focal parameter (based on white and gray matter in the frontal lobe). We need more studies using structural and metabolic brain imaging techniques, such as measurement of frontal lobe volume or interhemispheric fissure enlargement and ^{31}P-MRS using chemical shift imaging (CSI) to confirm and extend this finding.

The limitations of this preliminary study include a relatively small sample size, potentially confounding effects of neuroleptic medication (although the effects were not statistically significant) and the exclusive use of VBR measurements to assess ventricular enlargement. Neuroleptics in particular may influence PME and PDE results via possible alterations of phosphodiesterase and/or phospholipase A^1/A^2 activity, since two more recent studies showed changes in levels of phosphorus metabolites during neuroleptic treatment of schizophrenia (Fukuzako et al. 1999b; Volz et al. 1999). We should mention that, in this preliminary study, we substituted computed tomography (CT) in a clinical setting for magnetic resonance imaging (MRI) to measure the VBR. In a more recent review, however, McCarley et al. (1999) described that fully 77 % of the 43 MRI studies reported enlarged lateral ventricles, and this 77 % was about the same as the earlier literature on CT studies (75 %). Other methodological problems associated with ^{31}P-MRS have been described in detail in our previous reports (Shioiri et al. 1996, 1997) and, in brief, include medication effects, heterogeneity of tissue in the voxel of interest (VOI), limited spatial resolution of ^{31}P-MRS, and signal contamination from outside the VOI. In this preliminary study, only a schizophrenic sample of patients was investigated, and we did not include a control sample of healthy volunteers. However, we had already examined the relationship between brain phosphorous metabolism and ventricular enlargement in 60 normal control subjects and found no association (Kato et al. 1994). Despite these limitations, we believe the findings merit further study in a larger population of unmedicated patients.

References

American Psychiatric Association (1994) Diagnostic and Statistical Manual of Mental Disorders. 4th ed. Washington, DC: American Psychiatric Association Press

Andreasen NC, Oslen SA, Dennert JW, Smith MR (1982) Ventricular enlargement in schizophrenia: relationship to positive and negative symptoms. Am J Psychiatry 139: 297–302

Bottomley PA, Foster TB, Darrow RD (1984) Depth-resolved surface-coil spectroscopy (DRESS) for in vivo ^{1}H,^{31}P and ^{13}C NMR. J Magn Reson 59: 338–342

BuchliR Duc CO, Martin E, Boesinger P (1994) Assessment of absolute metabolite concentrations in human tissue by 31P MRS in vivo. Part I: cerebrum, cerebellum, cerebral gray and white matter. Magn Reson Med 32: 447–452

Cady EB (1990) Clinical Magnetic Resonance Spectroscopy. New York: Plenum Press

Campbell ID, Dobson CM, Williams RJP, Xavier AV (1973) Resolution enhancement of protein PMR spectra using the difference between a broadened and a normal spectrum. J Magn Reson 11: 172–181

Daniel DG, Goldberug TE, Gibbons RD, Weinberger DR (1991) Lack of bimodal distribution of ventricular size in schizophrenia. Biol Psychiatry 30: 887–903

Dawson RMC (1985) Enzymatic pathways of phospholipid metabolism in the nervous system. In: Eichberg J (ed) Phospholipids in Nervous Tissue. New York: Wiley, pp 45–78

Deicken RF, Calabrese G, Merrin EL, Meyerhoff DJ, Dillon WP, Weiner MW, Fein G (1994) ^{31}Phosphorus magnetic resonance spectroscopy of the frontal and parietal lobes in chronic schizophrenia. Biol Psychiatry 36: 503–510

DeLisi LM, Sakuma M, Tew W, Kushner M, Hoff AL, Grimson R (1997) Schizophrenia as a chronic active brain process: a study of progressive brain structural change subsequent to the onset of schizophrenia. Psychiatry Res Neuroimaging 74: 129–140

Fujimoto T, Nakano T, Takano T, Hokazono Y, Asakura T, Tsuji T (1992) Study of chronic schizophrenics using 31P magnetic resonance chemical shift imaging. Acta Psychiatr Scand 86: 455–462

Fukuzako H, Fukuzako T, Hashiguchi T, Kodama S, Takigawa M, Fujimoto T (1999a) Changes in levels of phosphorus metabolites in temporal lobes of drug-naive schizophrenic patients. Am J Psychiatry 156: 1205–1208

Fukuzako H, Fukuzako T, Kodama S, Hashiguchi T, Takigawa M, Fujimoto T (1999b) Haloperidol improves membrane phospholipid abnormalities in temporal lobes of schizophrenic patients. Neuropsychopharmacology. 21: 542-549

Gelenberg AJ (1983) The Practitioner Guide to Psychoactive Drugs. In: Basuk EL, Schoonover SC and Gelenberg AJ (eds) New York: Plenum Publishing

Hinsberger AD, Williamson PC, Carr TJ, Stanley JA, Drost DJ, Densmore M, MacFabe GC, Montemurro DG (1997) Magnetic resonance imaging volumetric and phosphorus 31 magnetic resonance spectroscopy measurements in schizophrenia. J Psychiatry Neurosci 22: 111–117

Kato T, Shioiri T, Murashita J, Hamakawa H, Inubushi T, Takahashi S (1994) Phosphorus-31 magnetic resonance spectroscopy and ventricular enlargement in bipolar disorder. Psychiatry Res Neuroimaging 55: 41–50

Kato T, Shioiri T, Murashita J, Hamakawa H, Inubushi T, Takahashi S (1995) Lateralized abnormality of high-energy phosphate and bilateral reduction of phosphomonoester measured by phosphorus-31 magnetic resonance spectroscopy of the frontal lobes in schizophrenia. Psychiatry Res Neuroimaging 61: 151–160

Kato T, Shioiri T, Murashita J, Inubushi T (1997) Phosphorus-31 magnetic resonance spectroscopic observations in 4 cases with anorexia nervosa. Prog Neuropsychopharmacol Biol Psychiatry 21: 719–724

Keshavan MS, Sanders RD, Pettegrew JW, Dombrowsky SM, Panchalingam KS (1993) Frontal lobe metabolism and cerebral morphology in schizophrenia: 31P MRS and MRI studies. Schizophr Res 10: 241–246

Kilby PM, Allis JL, Radda GK (1990) Spin-spin relaxation of the phosphodiester resonance in the 31P NMR spectrum of human brain: the determination of the concentrations of phosphodiester components. FEBS Letters 272: 163–165

Lim KO, Tew W, Kushner M, Chow K, Matsumoto B, DeLisi LE (1996a) Cortical gray matter volume deficits in patients with first-episode schizophrenia. Am J Psychiatry 153: 1548–1553

Lim KO, Harris D, Beal M, Minn K, Hoff A, Csernansky J, Faustman W, Marsh L, Sullivan EV, Pfefferbaum A (1996b) Gray matter volume deficits in young onset schizophrenia are independent of age of onset. Biol Psychiatry 40: 4–13

McCarley RW, Wible CG, Frumin M, Hirayasu Y, Levitt JJ, Fischer IA, Shenton ME (1998) MRI anatomy of schizophrenia. Biol Psychiatry 45: 1099–1119

Mozley PD, Gur RE, Resnick SM, Shtasel DL, Richard J, Kohn M, Grossman R, Herman G, Gur RC (1994) Magnetic resonance imaging in schizophrenia: relationship with clinical measures. Schizophr Res 12: 195–203

Nair TR, Christensen JD, Kingsbury SJ, Kumar NG, Terry WM, Garver DL (1997) Progression of cerebroventricular enlargement and the subtyping of schizophrenia. Psychiatry Res Neuroimaging 74: 141–150

Pearlson GD, Kim WS, Kubos KL, Moberg PJ, Jayaram G, Bascom MJ, Chase GA, Goldfinger AD, Tune LE (1989) Ventricular-brain ratio, computed tomographic density and brain area in 50 schizophrenics. Arch Gen Psychiatry 46: 690–697

Pettegrew JW, Keshavan MS, Panchalingam K, Strychor S, Kaplan DB, Tretta RN, Allen M (1991) Alterations in brain high-energy phosphate and membrane phospholipid metabolism in first-episode, drug-naive schizophrenics. Arch Gen Psychiatry 48: 563–568

Potwarka JJ, Drost DJ, Williamson PC, Carr T, Canaran G, Rylett WJ, Neufeld RW (1999) A 1H-decoupled 31P chemical shift imaging study of medicated schizophrenic patients and healthy controls. Biol Psychiatry 45: 687–693

Ron M, Harvey I, Lewis S, Murray R (1992) Diffuse brain abnormality in schizophrenia. Schizophr Res 7: 1–45

Sappey-Marinier D, Hubesch B, Matson GB, Weiner MW (1992) Decreased phosphorus metabolite concentrations and alkalosis in chronic cerebral infarction. Radiology 182: 29–34

Schlaepfer TE, Harris GJ, Tien AY, Peng LW, Lee S, Federman EB, Chase GA, Barta PE, Pearlson GD (1994) Decreased regional cortical gray matter volume in schizophrenia. Am J Psychiatry 151: 842–848

Shioiri T, Kato T, Inubushi T, Murashita J, Takahashi S (1994) Correlations of ^{31}P-MRS-measured phosphomonoester in the frontal region and negative symptoms in schizophrenia. Psychiatry Res Neuroimaging 55: 223–235

Shioiri T, Kato T, Murashita J, Hamakawa H, Takahashi S (1996) High-energy phosphate metabolism in the frontal lobes of patients with panic disorder detected by phase-encoded ^{31}P-MRS. Biological Psychiatry 40: 785–793

Shioiri T, Someya T, Murashita J, Kato T, Hamakawa H, Fujii K, Inubushi T (1997) Multiple regression analysis of relationship between the frontal lobe phosphorus metabolism and clinical symptoms in patients with schizophrenia. Psychiatry Res Neuroimaging 76: 113–122

Stanley JA, Williamson PC, Drost DJ, Carr TJ, Rylett RJ, Morrison-Stewart S, Thompson RT (1994) Membrane phospholipid metabolism and schizophrenia: an in vivo ^{31}P-MR spectroscopy study. Schizophr Res 13, 209–215

van der Knaap MS, van der Grond J, Luyten PR, den Hollander JA, Nauta JJ, Valk J (1992) 1H and 31P magnetic resonance spectroscopy of the brain in degenerative cerebral disorders. Ann Neurol 31: 202–211

Volz H-P, Rzanny R, Rossger G, Hubner G, Kreitschmann-Andermahr I, Kaiser AK, Sauer H (1997) Decreased energy-demanding processes in the frontal lobes of schizophrenis due to neuroleptics? A ^{31}P-magneto-resonance spectroscopic study. Psychiatry Res Neuroimaging 76:123–129

Volz H-P, Rzanny R, Rossger G, Hubner G, Kreitschmann-Andermahr I, Kaiser AK, Sauer H (1998) ^{31}Phosphorus magnetic resonance spectroscopy of the dorsolateral prefrontal region in schizophrenics: a study including 50 patients and 36 controls. Biol Psychiatry 44: 399–404

Volz HP, Rossger G, Riehemann S, Hubner G, Maurer I, Wenda B, Rzanny R, Kaiser WA, Sauer H (1999) Increase of phosphodi-

esters during neuroleptic treatment of schizophrenics: a longitudinal 31P-magnetic resonance spectroscopic study. Biol Psychiatry. 45: 1221–1225

Williamson P, Drost D, Stanley J, Carr T, Morrison S, Merskey H (1991) Localized phosphorous-31 magnetic resonance spectroscopy in chronic schizophrenic patients and normal controls. Arch Gen Psychiatry 48: 578

Wurthmann C, Bogerts B, Falkai P (1995) Brain morphology assessed by computed tomography in patients with geriatric depression, patients with degenerative dementia, and normal control subjects. Psychiatry Res Neuroimaging 61: 103–111

Zipursky RB, Lim KO, Sullivan EV, Brown BW, Pfefferbaum A (1992) Widespread cerebral gray matter volume deficits in schizophrenia. Arch Gen Psychiatry 49: 195–205