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Interregional correlation of cerebral glucose metabolism in unmedicated schizophrenia

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Abstract

To investigate metabolic relationships between different brain regions in schizophrenia, we measured regional brain metabolism using positron emission tomography (PET) and [^{18}F]fluorodeoxyglucose (FDG) in 15 unmedicated schizophrenic patients and 15 healthy subjects. We analyzed correlations between glucose metabolism data of multiple brain regions using factorial analysis and correlation coefficient comparisons. Absolute regional intercorrelations in schizophrenic brains were found to be significantly stronger than in controls, in relationship to the greater variability of metabolic rates in schizophrenic patients. Variability of normalized metabolic rates and regional intercorrelations were not significantly different between schizophrenic patients and control subjects. We conclude that a global metabolic factor accounts for the variability of metabolic data in untreated schizophrenia.

Keywords: Schizophrenia; PET-FDG; Metabolic interregional correlations.

1. Introduction

For 10 years, studies on brain glucose metabolism in schizophrenic patients have resulted in conflicting findings. Some studies using positron emission tomography (PET) with [^{18}F]fluorodeoxyglucose (FDG) have demonstrated decreased whole brain metabolism (Volkow et al., 1987). Some PET groups reported frontal lobe hypometabolism (hypofrontality) (Buchsbaum et al., 1982) in contrast to other groups who did not find these modifications (An-dreasen et al., 1992) and described increased frontal lobe metabolism (Szechtman et al., 1988), reduced parietal glucose metabolism (Cleghorn et al., 1989), bilateral hypertemporality (De Lisi et al., 1989) or reduced metabolism in hippocampus and anterior cingulate cortex (Tamm-inga et al., 1992). The aim of these studies was to reveal glucose metabolic disturbances in specific cerebral regions, such as the frontal and temporal lobes, which have been suspected to participate in the physiopathology of schizophrenia (Weinberger, 1988; Roberts, 1990). As an example, some studies (Andreasen et al., 1992; Buchsbaum et al., 1990) described hypofrontality which is defined either as a reduction in absolute local cerebral metabolic rate of glucose (CMRglu) in the frontal lobe or, more frequently, as a frontal hypometabolism relative to other brain areas. In the latter case, the choice of brain regions of reference is a major issue. This choice is usually based on a priori hypotheses of either normality in the region of reference or disturbances of metabolic relationships between brain regions suspected of being specifically implicated in schizophrenia. Based on this kind of analysis some researchers have found schizophrenic patients to have a reduced cortico-subcortical gradient (Szechtman et al., 1988) or a decreased antero-posterior gradient of their hemispheric cortical metabolism (Buchsbaum et al., 1984). Another approach to brain metabolism in schizophrenia would be to study the general relationships between all major brain areas (Clark et al., 1984). The use of this kind of analysis lies in the fact that there is no definite clue for the implication of one particular cerebral region in the pathogeny of schizophrenia. On the contrary, there are pharmacological clues for imbalances in neurotransmitter or neuromodulator systems with widespread effects on cortical and subcortical synaptic activity (Grace, 1991). In normal subjects, the existence of correlations between glucose metabolic rates of selected brain regions is well demonstrated, suggesting the existence of functional relationships between regions as well as patterns of functional systems (Metter et al., 1984a). In a condition with reduced influence of the modulatory dopaminergic system such as Parkinson's disease, correlations between glucose metabolic activities are decreased compared to controls. In Alzheimer's disease, regional interactions appear to be increased, probably in

relationship to neuronal loss and reduction of metabolic activity (Metter et al., 1984b). One study using factor analysis demonstrated a frontal and a subcortical factor that discriminated between normal subjects and medicated schizophrenic patients, but the level of correlation between regional CMRglu values was not different in the two groups at rest and during an activation task (Volkow et al., 1986). CMRglu interregional correlations have been recently related to clinical symptoms in schizophrenia (Friston et al., 1992), but in that study the level of correlation in the schizophrenic patients was not compared to data in normal subjects.
The aim of the present study is thus, using interregional correlations analysis, to compare unmedicated schizophrenic patients and normal subjects for metabolic relationships between major brain regions.

2. Experimental procedure

2.1. Subjects

Schizophrenic patients were recruited from inpatients (n = 13) and outpatients clinics (n=2) of the Department of Psychiatry at Erasme Hospital. This group was composed of 10 men and 5 women with a mean age±SD of 26.9±8 years. All patients underwent a structural interview with the Schedule for Affective Disorders and Schizophrenia (SADS) and met DSM-III-R criteria for subchronic (n = 6) or chronic (n=9) schizophrenia. The distribution of types was as follow: undifferenciated, n=7; paranoid, n = 8. None of our patients ever met criteria for drug or alcohol abuse. Evaluation was completed on the day of the PET study by:
- The Andreasen's scales for the assessment of positive and negative symptoms (positive mean score ±SD: 51.9±28.1; negative mean score±SD: 59.5±19.3).
- The 18-items Brief Psychiatric Rating Scale (BPRS) (mean score±SD: 56±14.4).
- The Edinburgh Handedness Inventory (right-handed 12; left-handed 2; ambidextrous 1).

Twelve patients had never received neuroleptics and the three remaining were withdrawn for more than 6 months. All patients were free of any other medication for more than 15 days. Medical screenings consisting of physical and neurological examination, clinical laboratory tests (cell blood count, blood chemistry, liver function tests, thyroid screening), electrocardiogram and electroencephalogram were normal in all patients.
Fifteen right-handed age-matched (mean age±SD: 28.4±7 years) normal volunteers (9 men and 6 women) participated in the study. They did not report familial or personal psychiatric disorders and had no history of medical or neurological disease, cranial trauma, drug or alcohol abuse. All 30 subjects gave informed consent after the procedure had been fully explained.

2.2. Scan procedure

The PET investigation was performed in a quiet and dimly lighted room. Each subject remained in a supine resting state with eyes closed. Each subject received an intravenous bolus of 5-6 mCi FDG. Fifteen seconds to 50 min after intravenous injection, 21 serial blood samples were taken from a radial artery. Blood samples were centrifuged and plasma was counted in a gamma counter. Glucose concentration was determined in plasma of 4 blood samples and used to determine CMRglu values. The activity of the tracer in the brain was measured with an 8-ring PET camera (CTI-Siemens 933-08-12, Knoxvil-le, TN) giving fifteen 7-mm-thick adjacent slices scanning the whole brain. The spatial resolution of the images is 5 mm full width at half maximum.
The subject was placed in the PET camera so as to obtain slices parallel to the canthomeatal line. Attenuation correction was calculated by means of an algorithm using a skull-fitting, operator-positioned ellipse and a uniform absorption coefficient of $0.095cm^{-1}$. The 20 min emission scan was started 40 min after the FDG injection. During this scan, the subject's immobility was checked with the help of laser beams corresponding to lines drawn on the subject's face.
Every day, the PET camera was calibrated to convert brain counts into brain radioactivity content. Plasma and brain radioactivity were corrected for decay.

2.3. Glucose metabolic rate quantification

Using emission scan data, plasma radioactivity time course and plasma glucose concentration, CMRglu was calculated with the CTI-Siemens software base according to the model of Sokoloff et al. (1977) adapted by Phelps et al. (1979). The lumped constant, which corrects for the differences in transport and phosphorylation rates of glucose and FDG, was assumed to be 0.42.
We delineated 20 regions of interest (ROI) on PET slices, symmetrically in both hemispheres,

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following a template based on the human brain stereotaxic atlas of Talairach and Tournoux (1988). Regions were drawn by a collaborator blind to the subject's diagnosis. Ten of the 40 ROI were defined in the frontal cortex, 4 in the parietal cortex, 6 in the temporal cortex, 6 in the cingulate cortex, 4 in the occipital cortex and 2 in the cerebellar cortex.
Finally, ROI were defined in the caudate nucleus, putamen, thalamus and ventral striatum. Relative CMRglu values were calculated by dividing each ROI CMRglu value by the weighted mean of the ipsilateral ROI CMRglu values calculated as follows $\Sigma(m \times p)/\Sigma p$, m representing the mean value of CMRglu in each ROI and p the number of pixel in each ROI.

Fig. 1. Correlation coefficient values (r) between absolute CMRglu values in 20 brain regions of the left hemisphere, in schizophrenic patients (A) and in control subjects (B).

1	1																		
													(A) SCHIZOPHRENIC PATIENTS Absolute values						
2	.82	1																	
3	.93	.89	1																
4	.90	.89	.95	1															
5	.93	.83	.94	.96	1														
6	.93	.90	.94	.93	.93	1													
7	.90	.85	.93	.98	.96	.92	1												
8	.89	.89	.91	.98	.95	.92	.97	1											
9	.80	.97	.84	.85	.79	.87	.82	.84	1										
10	.87	.98	.89	.90	.85	.91	.87	.90	.99	1									
11	.87	.88	.90	.96	.91	.88	.96	.97	.88	.91	1								
12	.85	.92	.89	.93	.90	.88	.90	.93	.92	.93	.94	1							
13	.89	.96	.92	.94	.92	.93	.90	.93	.96	.98	.94	.98	1						
14	.92	.93	.93	.96	.93	.94	.94	.97	.90	.95	.96	.95	.97	1					
15	.90	.94	.93	.94	.94	.94	.90	.92	.93	.95	.91	.97	.98	.96	1				
16	.89	.88	.90	.93	.93	.94	.89	.91	.83	.88	.87	.89	.92	.94	.96	1			
17	.84	.89	.87	.93	.92	.89	.92	.94	.85	.89	.91	.93	.93	.93	.94	.94	1		
18	.91	.89	.91	.96	.94	.94	.94	.95	.84	.90	.90	.92	.92	.94	.95	.96	.94	1	
19	.89	.89	.91	.94	.94	.96	.92	.94	.85	.90	.90	.90	.93	.96	.95	.98	.96	.95	1
20	.89	.90	.88	.83	.84	.88	.82	.82	.86	.89	.79	.87	88	.88	.93	.89	.87	.89	.87	1
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	18	17	18	19	20
1	1																		
													(B) CONTROL SUBJECTS Absolute values						
2	.26	1																	
3	.61	.56	1																
4	.60	.20	.54	1															
5	.65	.15	.15	.43	1														
6	.57	.47	.65	.52	.41	1													
7	.03	.51	.42	.34	.22	.05	1												
8	.12	.55	.35	.46	.42	.09	.75	1											
9	.64	.18	.40	.41	.09	.23	.10	.25	1										
10	.01	.09	.04	.60	.26	.44	.56	.67	.03	1									
11	.48	.17	.10	.61	.32	.29	.64	.63	.44	.59	1								
12	.50	.09	.11	.84	.48	.22	.69	.71	.29	.62	.79	1							
13	.71	.07	.55	.91	.52	.65	.43	.52	.55	.61	.63	.80	1						
14	.44	.06	.07	.58	.45	.08	.74	.71	.34	.49	.73	.84	.65	1					
15	.65	.14	.28	88	.55	.36	.63	.70	.47	.58	.75	.96	.91	.78	1				
16	.62	.06	.42	.67	.73	.36	.36	.57	.35	.39	.27	.66	.81	.58	.79	1			
17	.64	.11	.37	.66	.53	.28	.15	.43	.68	.15	.38	.47	.64	.30	.62	.62	1		
18	.53	.22	.46	.88	.64	.67	.28	.44	.25	.65	.46	.65	.82	.40	.73	.69	.71	1	
19	.49	.00	.45	.67	.60	.72	.17	.31	.15	.56	.32	.45	.70	.09	.60	.63	.58	.86	1
20	.87	.47	.73	.66	.50	.73	.10	.07	.60	.06	.38	.36	.68	.25	.51	.44	.69	.68	.55	1
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	18	17	18	19	20

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Correspondence between region number and Brodmann area: l=area 6; 2=area 7; 3=area 40; 4=area 9; 5 = area 24; 6=area 29-30-23-31; 7=area 10-46; 8=area 10-32; 9=medial area 17-18-19; 10=lateral area 17-18-19; ll=area 42-22; 12=caudate; 13 = thalamus; 14=area 21; 15=putamen; 16=ventral striatum; 17=area 11; 18 = area 25; 19=temporal inferior cortex; 20=cerebellar cortex.

2.4. Statistical analysis

Metabolic relationships between brain regions were studied by examining region-to-region correlations of CMRglu in schizophrenics and in controls. Intercorrela-tions between the 20 left regional CMRglu and between the 20 right regional CMRglu were performed, in absolute and in normalized values. Factorial analyses were per-formed, once for the left and once for the right regional absolute and normalized CMRglu. The method used for factor extraction is principal component analysis. The number of factors retained is determined by considering the only factors that account for variances greater than 1. In order to identify factors that are substantively meaning- ful, the varimax rotation method was applied. Multivariate test of Hotelling was performed to test the equality of 20 left and right ROI means between control subjects and schizophrenic patients. The homogeneity of variances was tested by Bartlett-Box F-test for each ROI individually (the multivariate Box's M-test for homogeneity of variances leads to a singular variance-covariance matrix).

3. Results

For the left absolute CMRglu values, the factorial analysis indicated that one principal factor accounted for 91.7% of the total variance in the group of schizophrenic patients whereas 5 principal factors were necessary to account for 90.7% of the total variance in controls (eigenvalue >1). Frontal regions were the main components of the first factors retained by the factorial analysis in the control group. The correlation coefficients are presented in correlation matrix form (Fig. 1). As shown in Fig. 1, intrahemispheric correlations between the 20 left regional absolute CMRglu values were stronger in schizophrenic subjects than in controls for a large number of regions. In the right hemisphere, one principal factor accounts for 89% of the total variance in schizophrenicsand 5 principal factors account for 90.5% of the total variance in controls (eigenvalue >1).
For left normalized CMRglu values, 6 principal factors accounted for 82% of the total variance in the schizophrenic group and 7 principal factors accounted for 89% of the total variance in controls. First factors in schizophrenic patients were mainly composed of frontal regions in contrast with the heterogeneous composition of factors in control subjects. The correlation coefficients are presented in Fig. 2. In the right hemisphere, 6 principal factors accounted for 85% of the total variance in the group of schizophrenic patients and in the control group. Regional CMRglu means, in absolute or normalized values, were not different between groups (all $P>0.45$). In absolute values. an inhomogeneity of variances was found in 17 left regions and 14 right regions (threshold at $P<0.05$) (Table 1).After normalization, an homogeneity of variances was found in 17 left regions and 17 right regions (threshold at $P<0.05$) (Table 2).

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Fig. 2. Correlation coefficient values (r) between normalized CMRglu values in 20 brain regions of the left hemisphere, in schizophrenic patients (A) and in control subjects (B).

(A) SCHIZOPHRENIC PATIENTS Normalized values

1	1																			
2	.16	1																		
3	.26	.11	1																	
4	.23	.35	.14	1																
5	.04	.69	.17	.38	1															
6	.29	.17	.17	.25	.08	1														
7	.11	.52	.00	.70	.37	.18	1													
8	.08	.29	.35	.59	.18	.15	.61	1												
9	.16	.58	.06	.32	.32	.18	.38	.48	1											
10	.02	.53	.20	.16	.20	.21	.35	.41	.91	1										
11	.03	.37	.27	.49	.04	.48	.63	.68	.28	.33	1									
12	.20	.10	.25	.01	.10	.43	.11	.04	.30	.18	.19	1								
13	.07	.23	.35	.38	.14	.14	.63	.21	.50	.40	.00	.53	1							
14	.21	.10	.22	.09	.06	.08	.01	.48	.03	.12	.45	.10	.24	1						
15	.02	.00	.43	.57	.04	.01	.61	.35	.05	.09	.31	.38	.52	.05	1					
16	.01	.08	.30	.05	.11	.23	.22	.02	.32	.22	.23	.14	.05	.18	.48	1				
17	.37	.30	.68	.08	.13	.33	.17	.37	.39	.42	.17	.06	.11	.04	.16	.45	1			
18	.10	.24	.48	.28	.01	.08	.19	.42	.50	.44	.03	.12	.30	.02	.17	.50	.43	1		
19	.04	.18	.51	.09	.14	.27	.00	.29	.52	.57	.11	.36	.16	.24	.23	.67	.62	.43	1	
20	.39	.33	.05	.67	.33	.15	.45	.46	.03	.04	.53	.12	.15	.11	.48	.23	.04	.13	.05	1
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20

(B) CONTROL SUBJECTS Normalized values

1	1																			
2	.03	1																		
3	.20	.62	1																	
4	.46	.25	.20	1																
5	.41	.02	.24	.07	1															
6	.01	.28	.36	.32	.18	1														
7	.36	.35	.25	.22	.06	.41	1													
8	.22	.44	.18	.10	.25	.46	.69	1												
9	.04	.01	.28	.34	.15	.17	.07	.06	1											
10	.50	.04	.16	.01	.33	.22	.46	.46	.39	1										
11	.06	.39	.48	.20	.14	.21	.37	.31	.11	.19	1									
12	.09	.15	.02	.08	.02	.12	.58	.55	.05	.20	.40	1								
13	.09	.27	.22	.05	.18	.51	.09	.02	.38	.31	.11	.40	1							
14	.13	.33	.48	.26	.21	.34	.41	.46	.03	.07	.46	.42	.17	1						
15	.09	.44	.11	.04	.05	.07	.31	.31	.33	.15	.44	.65	.69	.34	1					
16	.11	.18	.05	.08	.49	.03	.27	.10	.06	.43	.01	.39	.22	.19	.10	1				
17	.22	.31	.23	.28	.29	.20	.11	.05	.26	.23	.02	.13	.04	.01	.00	.47	1			
18	.04	.17	.22	.41	.21	.10	.25	.23	.42	.04	.07	.10	.10	.24	.10	.24	.47	1		
19	.05	.23	.05	.04	.23	.32	.29	.30	.27	.13	.26	.18	.03	.67	.05	.30	.27	.51	1	
20	.29	.28	.25	.09	.14	.49	.66	.76	.41	.65	.08	.35	.28	.39	.07	.09	.13	.06	.19	1
	I	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20

Correspondence between region number and Brodmann area: l=area 6; 2=area 7; 3=area 40; 4=area 9; 5=area 24; 6=area 29-30-23-31; 7=area 10-46; 8=area 10-32; 9=medial area 17-18-19; 10=lateral area 17-18-19;11=area 42-22; 12=caudate; 13=thalamus; 14=area 21; 15=putamen; 16=ventral striatum; 17=area 11; 18=area 25; 19=temporal inferior cortex; 20=cerebellar cortex.

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Table 1
Coefficients of variability (SD/mean) of absolute glucose metabolic rates in 40 regions of interest

Structure		Normal controls	Schizophrenic patients	Bartlett box (P-value)
Area 6	L	0.136	0.198	0.098
	R	0.162	0.238	0.141
Area 9	L	0.105	0.208	0.002
	R	0.089	0.222	0.000
Area 10-32	L	0.106	0.181	0.009
	R	0.110	0.169	0.066
Area 10-46	L	0.115	0.199	0.028
	R	0.079	0.168	0.004
Area 11	L	0.107	0.183	0.008
	R	0.101	0.170	0.040
Area 7	L	0.128	0.245	0.040
	R	0.129	0.292	0.006
Area 40	L	0.132	0.245	0.023
	R	0.119	0.252	0.001
Area 21	L	0.109	0.2009	0.001
	R	0.098	0.179	0.002
Area 42-22	L	0.127	0.179	0.112
	R	0.092	0.190	0.003
Temporal inferior cortex	L	0.095	0.165	0.025
	R	0.097	0.151	0.086
Area 24	L	0.135	0.218	0.003
	R	0.134	0.201	0.010
Area 25	L	0.123	0.177	0.080
	R	0.130	0.177	0.119
Area 29-30-23-31	L	0.131	0.234	0.013
	R	0.120	0.223	0.006
L. area 17-18-19	L	0.093	0.405	0.000
	R	0.092	0.377	0.000
M. area 17-18-19	L	0.110	0.407	0.000
	R	0.116	0.406	0.000
Thalamus	L	0.112	0.218	0.003
	R	0.114	0.226	0.002
Caudate	L	0.119	0.237	0.003
	R	0.119	0.231	0.000
Putamen	L	0.101	0.201	0.004
	R	0.105	0.190	0.010
Ventral striatum	L	0.099	0.201	0.022
	R	0.110	0.184	0.104
Cerebellar cortex	L	0.123	0.220	0.025
	R	0.119	0.185	0.086

L=left, R=right, L. = lateral, M.=median

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Table 2
Coefficients of variability (SD/mean) of normalized glucose metabolic rates in 40 regions of interest

Structure		Normal controls	Schizophrenic patients	Bartlett box (P-value)
Area 6	L	0.077	0.073	0.598
	R	0.097	0.061	0.057
Area 9	L	0.040	0.049	0.639
	R	0.034	0.055	0.039
Area 10-32	L	0.054	0.053	0.823
	R	0.083	0.064	0.208
Area 10-46	L	0.074	0.060	0.313
	R	0.060	0.068	0.768
Area 11	L	0.070	0.069	0.823
	R	0.064	0.059	0.639
Area 7	L	0.110	0.069	0.047
	R	0.098	0.096	0.658
Area 40	L	0.091	0.077	0.334
	R	0.053	0.077	0.088
Area 21	L	0.058	0.045	0.401
	R	0.039	0.066	0.052
Area 42-22	L	0.078	0.061	0.297
	R	0.048	0.080	0.111
Temporal inferior cortex	L	0.052	0.061	0.594
	R	0.055	0.061	0.608
Area 24	L	0.076	0.055	0.805
	R	0.096	0.078	0.691
Area 25	L	0.059	0.052	0.677
	R	0.064	0.085	0.354
Area 29-30-23-31	L	0.087	0.066	0.238
	R	0.077	0.058	0.284
L. area 17-18-19	L	0.046	0.157	0.000
	R	0.070	0.138	0.030
M. area 17-18-19	L	0.084	0.165	0.041
	R	0.063	0.173	0.002
Thalamus	L	0.045	0.041	0.706
	R	0.044	0.056	0.234
Caudate	L	0.064	0.066	0.593
	R	0.073	0.065	0.071
Putamen	L	0.042	0.040	0.678
	R	0.041	0.050	0.623
Ventral striatum	L	0.411	0.068	0.684
	R	0.412	0.081	0.859
Cerebellar cortex	L	0.094	0.096	0.754
	R	0.085	0.092	0.337

L=left, R=right, L. = lateral, M. = median.

4. Discussion

Intrasubject correlations between absolute local CMRglu values are significantly stronger in schizophrenic patients than in control subjects as revealed by factorial analysis. When CMRglu values are normalized using the weighted mean of the ipsilateral ROI CMRglu values, this effect disappears. Besides, the normalization procedure cancels the differences of variability found in most cerebral regions between schizophrenic patients and control subjects. Thus, the stronger interregional correlations in schizophrenic's absolute CMRglu values are probably due to a greater CMRglu variability which disappears after normalization. There is no valid statistical test for the comparison of correlation matrices with group differences in variability. The higher dispersion of CMRglu values in schizophrenics may be related to the variability in clinical symptoms or, possibly, to the nosographic heterogeneity of the schizophrenic syndrome. However, in our group of schizophrenic patients, outliers do not present any particular clinical characteristics compared to the other patients at the time of the

PET study. In our set of data, it is not possible to determine the influence of clinical presentation or schizophrenic type on CMRglu data variability, but this point could be analyzed in the future in a larger population of patients. Volkow et al. (1986) showed that 4 factors accounted for 72 and 69% of the total variance of relative metabolic values in normal subjects and neuro-leptized schizophrenic patients, respectively. Our study corroborates these results in normal and unmedicated schizophrenic subjects. These results indicate that a global metabolic factor, neutralized by the normalization procedure, has a more variable impact in schizophrenic patients than in control subjects. This global factor seems unrelated to the technical PET conditions which are identical in the two groups. The normalization procedure helps to reduce the impact of global effects on interregional correlations (McCrory and Ford, 1991). Our factorial analysis reveals the major influence of the frontal lobes on normalized CMRglu variability in schizophrenic patients but not in the control subjects. The major impact of the frontal metabolic activity on the brain metabolic pattern in schizophrenia provides another clue to the probable involvement of the frontal lobes in the pathophysiology of the disease (Williamson, 1987; Weinberger, 1988).

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