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Regional brain glucose metabolism in drug free schizophrenic patients and clinical correlates

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ABSTRACT – Regional brain glucose metabolism was investigated in healthy volunteers (n = 10) and in drug free schizophrenic patients (n = 20). The metabolism was determined by positron emission tomography (PET) with ^{11}C-glucose as the tracer. Diagnosis of schizophrenia was made according to RDC and DSM III. Eight patients had their first psychotic episode, four patients had a subchronic course and eight patients had a chronic course with an exacerberation of their illness. Computed tomography (CT) of the brain were made in all the subjects. Regions of interest (n = 35) were drawn on displayed CT images and the marked regions were transferred to the corresponding slice of the PET examination. The PET investigation was made in a dimly lit, quiet room with the eyes of the subject covered. The time course of the ^{11}C-glucose uptake was measured by a four ring PET scanner (PC-384-7B).

Metabolic rates of glucose varied greatly among the schizophrenic patients investigated. The variance was significantly greater than that of the controls in most regions. Decreases in mean levels of metabolic rates were related to patients with subchronic or chronic courses. Changes in metabolism were not related to previous duration of neuroleptic treatment of the patients. Left-right asymmetries were found in the temporal lobe (area 22) and the basal frontal cortex (area 11), the metabolic rates of the patients being lower on the left side compared to the controls. Asymmetry of the metabolic rate of the amygdala in hebephrenic patients was the opposite of that found in paranoid patients and controls. Negative correlations between regional metabolic rates and autistic or negative symptoms were found. Thus, the lower the metabolic rate was, the more autistic the patient. Metabolic rates were not correlated to atrophic changes of the brain.

No basis for a specific alteration in frontal cortical metabolism of schizophrenics was obtained. Changes in regional metabolic rates in schizophrenia are suggested to reflect disturbances in more general mechanisms which are of importance in neuronal function.

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In the pioneering work by Ingvar & Franzen (1) on cerebral blood flow in schizophrenic patients the hypothesis of frontal cortical dysfunction in schizophrenia was proposed. Chronic and elderly schizophrenic patients were found to have a hypofrontal distribution of cerebral blood flow in the left hemisphere while a hyperfrontal distribution was observed in controls (2). The more

autistic, catatonic or cognitively deteriorated the patient was the lower the frontal cerebral blood flow was found to be. Further studies with a similar technique (i.e. the use of Xenon-133 for measuring cerebral blood flow) and 18-F-2-deoxyglucose studies with positron emission tomography (PET) seemed to confirm the hypothesis of a hypofrontal pattern in schizophrenic patients (3–7). In later studies a lower metabolism or blood flow was found in frontal as well as in other cortical areas but no hypofrontal distribution (8–11). An imbalance between the left and right hemisphere has been suggested to be of importance in schizophrenia (12), and divergent asymmetries have been found in both blood flow (13) and metabolism (14, 15).

The results from the different studies mentioned above are not consistent. However, comparisons are difficult to make due to differences in methodology, selection of patients and experimental design. The importance of neuroleptic treatment was probably underestimated in earlier studies but has been shown to affect human brain glucose metabolism (10, 17). Furthermore, the concept of drug-free patients may include both patients in a stable phase of the disease, patients taken off drugs a couple of weeks before the PET investigation, as well as patients who relapsed in the psychosis following discontinuance of neuroleptic administration. Conditions under which the PET investigation are made may also affect the results since the subjects often have varying powers of concentration. The influence of these unspecific factors might be reduced by directing the attention of the subject to some specific test during the investigation. Differences in functional activities between groups might be observed that otherwise would be neglected under resting conditions (5, 13, 18). However, such studies must be interpreted with care, since a basic disturbance in the metabolism may be concealed by the changes in brain activity induced by the test.

Another major problem in comparing results from different research centers arises from the methods with which regions of interest were defined. Several factors have to be considered such as resolution of the camera, numbers and thickness of slices, the type of head fixation system and accessibility to computed tomographic (CT) facilities. One great advantage with the PET technique is the possibility to identify in the images both cortical and subcortical parts of the brain. However, the resolution of PET is rather low and unfortunately, regions of interest are not always determined by use of CT, but rather by automatic techniques with arbitrary definitions of the boundaries of the regions or by drawings made directly on the PET images.

The aim of the present PET study was to investigate regional brain glucose metabolism in drug free schizophrenic patients in need of hospital treatment. Regions of interest were defined according to their morphological appearance on CT images and transferred to the PET images. Relationships between clinical variables and metabolism were also investigated.

Methods

The protocol of the study was approved by the Ethics- and Isotope Committees of the Karolinska Hospital, Stockholm, Sweden.

Subjects

Patients admitted to the Psychiatric Clinic at the Karolinska Hospital for treatment were selected for the study. The Research Diagnostic Criteria (RDC) (19) and DSM III for schizophrenia had to be satisfied for inclusion in the study. Patients with organic brain disorder, somatic disease, prior head injury or infection of the central nervous system, previous or actual abuse of alcohol or narcotics were excluded. A total of 24 patients were recruited for the project. Two patients were later excluded when it was found that they did not fulfill all the diagnostic criteria, and another two unexpectedly refused to participate in the PET investigation. In all 20 patients (15 men and five women) fulfilled the protocol. Eight patients were in their first psychotic episode. According to DSM III, four patients had a subchronic course and eight patients had a chronic course of the illness with an exacerberation (Table 1). The total duration of illness was at most 10 years, and the maximal duration of neuroleptic treatment was approximately 6 years. The shortest duration

Table 1
Clinical description of schizophrenic patients

No.	Age/sex	DSM III types	Total duration of illness (years)	Number of episodes	Course of illness	Duration of actual episode prior to investigation (months)	Total duration on neuroleptics (months)	Duration without neuroleptics prior to investigation (months)
1.	34/F	U	3.0	2nd	SC exac.	0.5	0	-
2.	22/M	P	0.5	1st	SC	2.0	0	-
3.	26/F	H	3.0	4th	C exac.	0.75	33	0.75
4.	21/M	P	0.5	1st	SC	3.0	0	-
5.	33/M	H	8.0	3rd	C exac.	36.0	12	60
6.	41/M	P	10	3rd	C exac.	12.0	72	3.0
7.	29/F	P	2.3	4th	C exac.	1.0	11	2.0
8.	20/F	H	3.0	2nd	C exac.	5.0	3.0	24
9.	19/M	P	0.5	1st	SC	6.0	0	-
10.	35/M	P	0.5	1st	SC	6.0	0	-
11.	29/F	P	0.5	1st	SC	6.0	0	-
12.	22/M	H	1.8	3rd	SC exac.	0.5	15	3.0
13.	26/M	P	0.5	1st	SC	6.0	0	-
14.	26/M	H	1.8	3rd	SC exac.	3.0	9.0	6.0
15.	35/M	P	7.0	2nd	C exac.	12.0	2.0	54
16.	21/M	H	2.0	2nd	SC exac.	3.0	10	14
17.	29/M	U	0.5	1st	SC	3.0	0	-
18.	36/M	P	3.0	2nd	C exac.	12	0.7	36
19.	22/M	H	4.0	3rd	C exac.	9.0	1.5	17
20.	20/M	H	0.5	1st	SC	6.0	0	-

F = female; M = male; U = undifferentiated; P = paranoid; H = hebephrenic; SC = subchronic; C = chronic; exac. = exacerberation.

without neuroleptics prior to the PET investigation was 3 weeks (Table 1). Patients on depot neuroleptics had their last injection at least 6 months before the PET investigation. Subclassification according to DSM III gave the following number of subtypes: paranoid 10, hebephrenic eight and undifferentiated two patients. Due to anxiety or severe sleep disturbances in some of the patients it was neccessary to administer benzodiazepines to avoid neuroleptic treatment before the investigation. Thus, seven patients (of whom four had their first episode) received single doses of oxazepam (15–25 mg) or nitrazepam (5–10 mg) the week before the investigation. One of these patients received a regular medication of nitrazepam of 5–10 mg every second or third night, during several weeks before the PET investigation. In this patient absolute metabolic rates were not calculated since arterial blood samples were not obtained. Absolute and relative metabolic rates of these patients were not different from the rest of the patients.

The control subjects were 10 male healthy volunteers recruited from the neighbourhood of Stockholm. Their age was similar to that of the patients (controls 29 ± 6.2 (SD), range 22–41, patients 27 ± 6.5 (SD) range 19–41). The volunteers were investigated according to standardized protocols in order to exclude subjects with previous or actual psychiatric disturbances, or somatic diseases such as head injury, infection of the central nervous system, systemic disease or neurological disease. All subjects with a previous or actual abuse of alcohol or narcotics of any kind were excluded. Before each PET investigation patients and volunteers were checked with routine physical examination and analysis of blood chemistry reflecting liver, kidney or blood function. No abnormalities were found.

Measures of psychotic morbidity

Global rating of psychosis was made in order to determine the patients overall degree of mor-

bidity. Clinical morbidity was measured by using the comprehensive psychological rating scale (CPRS) (20). The CPRS consists of 65 items reflecting a wide spectrum of reported and observed psychopathological symptoms. Each item in the CPRS was scored by a psychiatrist according to a 7-point scale (range 0–3). A high score on an item corresponds to a pronounced psychopathology. All the patients were rated the day before or on the same day as the PET investigation. By selecting individual CPRS items different subscales were constructed, one for depressive symptoms (21), one for positive symptoms (22) and one for autistic or negative symptoms (Items no. 5: Inability to feel; 14: Lassitude; 45: Lack of appropriate emotion; 49: Withdrawal; 54: Reduced speech; 60: Slowness of movement).

Regions of interest

Computed tomography (CT) of the brain were made in all the subjects. A head fixation system was used consisting of a base plate rigidly attached to the patient's head by a plastic mould (23). This base plate and the plastic mould were also used for fixation during the PET investigation, so that the same positioning and slices of the brain were obtained at the two investigations. Displayed CT images were used for marking regions of interest with the aid of a cursor. These marked regions of interest were transferred to the corresponding slice obtained at the PET examination (Fig. 1). Most of the regions were drawn at more than one slice level. Cortical structures were drawn from anatomical landmarks in approximate agreement with Brodmann's definitions of cortical structures (24). Subcortical structures were drawn according to conventional anatomical criteria. The following regions were analyzed: Brodmann area 6 (premotor cortex), 8 (supplementary eye field), 9, 10 (prefrontal cortex), 11, 12 (orbital frontal cortex), 22 (superior temporal cortex), 23, 24 (limbic cortex or cingulum), 32 (medical frontal cortex), 39 + 40 (inferior parietal cortex), caudate nucleus, lentiform nucleus, thalamus, amygdala, hippocampus, mesencephalon, pons and vermis.

Fig. 1. To the left a CT scan of a healthy volunteer and to the right a PET scan of the same volunteer. Regions of interest were drawn on the CT image and the marked regions were transferred to the PET image. The following regions were marked at this slice level: Brodmann areas 10, 32 and 22, caudate, lenticular nucleus, thalamus.

PET procedure

The PET investigation was made in a dimly lit, quiet room with the eyes of the subject covered. Noise was dampened since the plastic mould covered the ears. An EEG was recorded to check that the subject did not fall asleep during the PET scanning. The tracer, ^{11}C-glucose was produced photosynthetically using green algae (25). Between 150 and 400 MBq of the tracer was injected intravenously as a bolus. The content of unlabelled glucose as well as ^{11}C-activity was determined in plasma from arteriolized venous blood (warming the hand) or arterial blood from the contralateral arm. The samples were measured in a well-counter.

The time course of the tracer uptake was measured by a four ring PET scanner (PC-384-7B) (26). The scanner has 96 detectors in each ring and accumulates data from seven image sections simultaneously covering an axial distance of 10 cm of the brain. In both the cross planes and direct planes the spatial resolution of the reconstructed images is 7.6 mm full-width at half maximum (FWHM). The slice thickness is 8.0–11.1 mm (FWHM) for cross slices and 11.5 mm (FWHM) for direct slices. The head was positioned so that almost the whole brain was covered with the seven slices, and so that the PET slices obtained were identical with the CT slices, thereby allowing the calculation of glucose metabolism in the regions of interest. The smallest regions (amygdala, hippocampus) had pixel numbers between 15 and 40 which are within the resolution limits of the scanner.

Glucose metabolism

In the calculation of regional glucose metabolism a three compartment model was applied. The tracer is considered to be either in arterial plasma as ^{11}C-glucose, in the tissue as ^{11}C-glucose (the precursor pool) or in the tissue as various ^{11}C labelled metabolic products (the metabolic pool) (27). From the last compartment there is a loss mainly in the form of ^{11}C-CO_2. The regional loss of tracer is not directly observable and must somehow be estimated. The average loss was calculated in experiments with monkeys where the arterio-venous difference in ^{11}C-CO_2 was measured as a function of time after an i.v. bolus injection of ^{11}C-glucose. Since the correction for ^{11}C-CO_2 increases with time the calculation of the metabolism was based only on blood and PET data sampled during the first 15 min of the investigation in order to avoid too large a correction and to obtain satisfactory statistics. At each point in time the observed tissue activity was corrected with the accumulated average loss of ^{11}C-CO_2 per unit mass of tissue allowing the calculation of glucose metabolism of each volume element in each subject (27, 28). Average values for cerebral metabolic rates of glucose (CMRglc) were subsequently calculated for each brain region.

The tracer kinetic model used to calculate the glucose metabolism is highly dependent on the input function of plasma glucose to the brain. Absolute regional glucose values were therefore compared only for the patients (n = 15) and the healthy volunteers (n = 9) from whom it was possible to obtain arterial blood samples. When arteriolized venous blood was used the input functions of plasma glucose to the brain varied greatly. To avoid bias in the selection of satisfactory plasma curves an operational definition was used: if venous samples were obtained only relative metabolic rates were used in the statistical analysis. Thus relative regional metabolic values (the ratio between the metabolic value of the region and the whole brain) were calculated in all the subjects.

Statistics

For comparison of differences between the two groups the two tailed t-test was used, adopted for either unequal or equal variances. The product moment correlation coefficient was used in the calculation of correlations. Analysis of variance (ANOVA) was used in comparisons between several groups.

Results

Absolute metabolic rates

No significant difference between the whole

Table 2
Comparison of cortical brain glucose metabolism in healthy volunteers and drug free schizophrenic patients

Brain region	Glucose metabolism (μmol/100 g × min)	
	Healthy volunteers (n = 9)	Patients (n = 15)
Brodmann 6		
dx	26.2 ± 3.10	23.6 ± 7.57 [1]
sin	25.5 ± 2.49	23.8 ± 8.14 [2]
Brodmann 8		
dx	26.2 ± 2.47	25.3 ± 7.39 (14)[2]
sin	25.9 ± 2.34	25.0 ± 7.67 (14)[2]
Brodmann 9		
dx	26.0 ± 2.55	23.2 ± 7.54 [2]
sin	25.5 ± 2.48	23.1 ± 7.63 [2]
Brodmann 10		
dx	25.6 ± 2.60	22.2 ± 7.12 [2]
sin	25.4 ± 2.74	22.2 ± 7.17 [2]
Brodmann 11		
dx	24.9 ± 2.49 (5)	26.5 ± 6.90 (5)
sin	28.2 ± 4.05 (5)	26.0 ± 8.73 (5)
Brodmann 12		
dx	25.2 ± 3.03 (7)	23.9 ± 8.31 (12)[1]
sin	26.4 ± 4.38 (7)	22.4 ± 8.35 (12)
Brodmann 22		
dx	24.6 ± 2.90	21.3 ± 6.64 [1]
sin	25.8 ± 2.85	20.8 ± 6.90 [1]*
Brodmann 23		
dx	28.0 ± 5.15	22.9 ± 5.69 (9)+
sin	27.9 ± 6.37	26.5 ± 8.57 (9)
Brodmann 24		
dx	21.2 ± 2.65	18.1 ± 7.17 (12)[2]
sin	22.6 ± 3.99	19.8 ± 7.95 (12)
Brodmann 32		
dx	26.5 ± 2.98	22.4 ± 6.25 [2]*
sin	27.5 ± 2.40	22.7 ± 7.30 [2]*
Brodmann 39 + 40		
dx	26.2 ± 3.08	22.7 ± 7.46 [1]
sin	26.3 ± 2.29	22.8 ± 7.78 [2]
Whole brain	22.5 ± 2.08	19.9 ± 6.34 [2]

Mean values ± S.D. The number of subjects within brackets if different from the table head. Two tailed t-test adopted for equal or unequal variances. P-values for F-ratios: [1] $P < 0.05$; [2] $P < 0.01$; and t-values + $P < 0.1$; * $P < 0.05$.

Table 3
Comparison of subcortical brain glucose metabolism in healthy volunteers and drug free schizophrenic patients

Brain region	Glucose metabolism (μmol/100 g × min)	
	Healthy volunteers (n = 9)	Patients (n = 15)
Caudate nucleus		
dx	21.8 ± 1.98	19.4 ± 6.75 [2]
sin	20.5 ± 1.63	19.5 ± 5.80 [2]
Lentiform nucleus		
dx	25.9 ± 3.97	21.6 ± 7.45
sin	25.8 ± 2.92	21.5 ± 6.98 [1]*
Thalamus		
dx	23.0 ± 3.23	20.9 ± 6.70 [1]
sin	23.0 ± 3.63	20.6 ± 6.35
Amygdala		
dx	19.5 ± 1.94 (5)	18.2 ± 6.81 (7)[1]
sin	23.2 ± 3.09 (5)	19.9 ± 6.76 (7)
Hippocampus		
dx	20.2 ± 3.75 (8)	18.8 ± 5.33 (13)
sin	20.6 ± 2.62 (8)	18.6 ± 5.60 (13)
Mesencephalon	18.9 ± 2.71	11.1 ± 5.78 (14)[1]
Pons	16.5 ± 1.42	15.7 ± 5.46 (13)[3]
Vermis	25.9 ± 2.46	22.8 ± 7.70 [2]

Mean values ± S.D. The number of subjects within brackets if different from the table head. Two tailed t-test adopted for equal or unequal variances. P-values for F-ratios: [1] $P < 0.05$; [2] $P < 0.01$; [3] $P < 0.001$. P-values for t-values; * $P < 0.05$.

brain glucose metabolism of the healthy volunteers and that of the patients was observed. However, significantly lower mean metabolic rates were found in the following regions in patients: area 22 left hemisphere, in area 32 bilaterally and in the left lentiform nucleus (Tables 2 and 3). In area 22 a significant interaction between groups and hemispheric side was found. The patients exhibited a lower metabolic rate in the left side than in the right side while the opposite asymmetry was observed for the controls (ANOVA F = 6.52, $P < 0.05$). The major difference between the two groups was that the variance of metabolic values for the patients was significantly greater in most of the regions (Tables 2, 3 and Fig. 2). For instance the lowest metabolic rate of the lentiform nucleus of the controls coincided with the mean value of the patients (Fig. 2). A significant relation between diagnostic subgroups (paranoid and hebephrenic patients) and lateralized metabolism for the amygdala was found. A higher

metabolism was observed in the left amygdala of the paranoid patients and in the right amygdala of the hebephrenics (ANOVA, F = 4.80, $P < 0.05$). The controls were similar to the paranoid group.

The chronic and subchronic patients with an exacerberation of the disease had a lower glucose metabolism in several regions than the controls and first episode patients (Table 4). There was also a tendency in subchronic and chronic patients towards lower metabolism of the left temporal area 22 and left amygdala

Table 4
ANOVA of differences in regional brain glucose metabolism between healthy controls, patients with their first psychotic episode and patients with two or several psychotic episodes

Variable	Group	F-ratio		Interpretation
		Lateral	Group*Lateral	
Brodmann 6	1.20	0.06	1.96	-
Brodmann 8	1.37	0.70	1.20	-
Brodmann 9	2.73+	0.47	0.28	E > = C > CP
Brodmann 10	2.74+	0.00	0.53	C = E > CP
Brodmann 22	2.75+	0.02	3.12+	C > E > CP; C:R < L E:R > = L CP:R > L
Brodmann 23	4.14*	2.46	0.69	C > E > = CP
Brodmann 24	0.89	5.03*	0.07	R < L
Brodmann 32	4.28*	1.18	0.25	C > = E > CP
Brodmann 39 + 40	2.48	0.30	1.09	-
Caudate nucleus	1.79	0.77	1.52	-
Lentiform nucleus	3.52*	0.02	0.04	C > = E > CP
Thalamus	2.46	0.98	1.88	-
Amygdala	2.28	7.52*	3.70+	R < L; C:R < L E:R < L CP: R > L
Hippocampus	3.54*	0.00	0.24	E > = C > CP

C = healthy controls (n = 9); E = 1st psychotic episode (n = 6); CP = Two or several psychotic episodes (n = 9); Lateral = right-left side interaction. Area 11 and 12 not analyzed due to the few number of subjects in one of the groups.
+ $P < 0.10$, * $P < 0.05$.

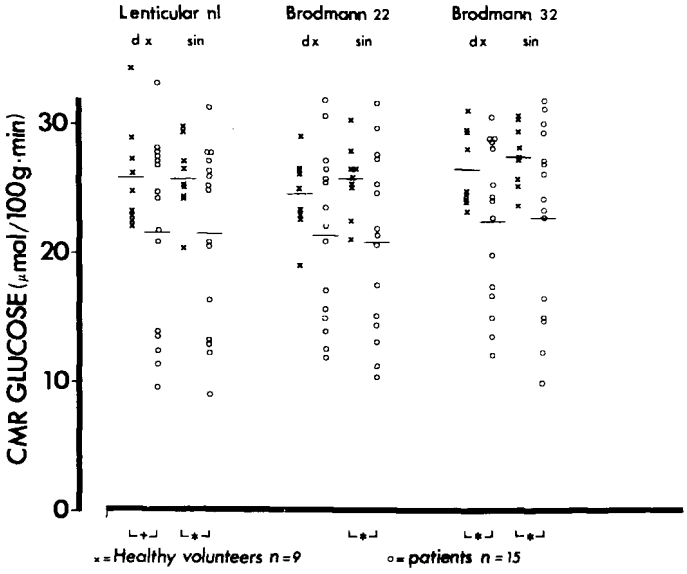

Fig. 2. Regional CMRglc in healthy volunteers and drug-free schizophrenic patients. Two tailed t-test adopted for equal or unequal variances, $+P < 0.1$, $*P < 0.05$.

Table 5
Comparison of relative cortical brain glucose metabolism in healthy volunteers and drug free schizophrenic patients

Brain region	Relative glucose metabolism	
	Healthy volunteers (n = 10)	Patients (n = 20)
Brodmann 6		
dx	1.17 ± 0.061	1.17 ± 0.085
sin	1.15 ± 0.070	1.17 ± 0.070
Brodmann 8		
dx	1.17 ± 0.064	1.23 ± 0.137 (19)[1]
sin	1.17 ± 0.112	1.19 ± 0.084 (19)
Brodmann 9		
dx	1.16 ± 0.080	1.14 ± 0.058
sin	1.15 ± 0.061	1.16 ± 0.087
Brodmann 10		
dx	1.14 ± 0.063	1.12 ± 0.070
sin	1.13 ± 0.063	1.11 ± 0.050
Brodmann 11		
dx	1.11 ± 0.054 (5)	1.20 ± 0.087 (8) +
sin	1.26 ± 0.174 (5)	1.17 ± 0.172 (8)
Brodmann 12		
dx	1.12 ± 0.091 (7)	1.17 ± 0.080 (17)
sin	1.17 ± 0.091 (7)	1.14 ± 0.083 (17)
Brodmann 22		
dx	1.09 ± 0.061	1.09 ± 0.100
sin	1.15 ± 0.051	1.06 ± 0.082 **
Brodmann 23		
dx	1.23 ± 0.196 (8)	1.23 ± 0.211 (12)
sin	1.23 ± 0.274 (8)	1.33 ± 0.253 (12)
Brodmann 24		
dx	0.95 ± 0.156	1.01 ± 0.205 (16)
sin	0.98 ± 0.183	1.02 ± 0.135 (16)
Brodmann 32		
dx	1.18 ± 0.100	1.16 ± 0.094
sin	1.22 ± 0.039	1.12 ± 0.090 [2]***
Brodmann 39 + 40		
dx	1.17 ± 0.056	1.12 ± 0.071 *
sin	1.16 ± 0.057	1.11 ± 0.071 +

Mean values ± S.D. The number of subjects within brackets if different from the table head. Two tailed t-test adopted for equal or unequal variances. P-values for F-ratios: [1] $P < 0.05$; [2] $P < 0.01$. P-values for t-values + $P < 0.10$, * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$.

Table 6
Comparison of relative subcortical brain glucose metabolism in healthy volunteers and drug free schizophrenic patients

Brain region	Relative glucose metabolism	
	Healthy volunteers (n = 10)	Patients (n = 20)
Caudate nucleus		
dx	0.95 ± 0.034	0.99 ± 0.996 [2]
sin	0.91 ± 0.050	1.00 ± 0.100 [1]**
Lentiform nucleus		
dx	1.13 ± 0.111	1.08 ± 0.077
sin	1.13 ± 0.063	1.08 ± 0.070 +
Thalamus		
dx	1.01 ± 0.099	1.04 ± 0.082
sin	1.01 ± 0.141	1.05 ± 0.101
Amygdala		
dx	0.81 ± 0.040 (6)	0.87 ± 0.142 (10)[1]
sin	0.96 ± 0.112 (6)	0.95 ± 0.110 (10)
Hippocampus		
dx	0.88 ± 0.110 (9)	0.94 ± 0.139 (18)
sin	0.92 ± 0.078 (9)	0.93 ± 0.087 (18)
Mesencephalon	0.81 ± 0.098	0.83 ± 0.094 (19)
Pons	0.73 ± 0.040 (9)	0.78 ± 0.088 (17)[1] +
Vermis	1.15 ± 0.036	1.14 ± 0.048

Mean values ± S.D. The number of subjects within brackets if different from the table head. Two tailed t-test adopted for equal or unequal variances. P-values for F-ratios: [1] $P < 0.05$; [2] $P < 0.01$. P-values for t-values + $P < 0.10$; ** $P < 0.01$.

than the other groups. A comparison was also made between patients with a total duration of neuroleptic treatment up to 3 months and those with a longer duration. No group differences were found. However, an interaction between duration of neuroleptic treatment and lateralization of metabolism was found with regard to amygdala. Similar to the controls the patients treated with neuroleptic compounds up to 3 months had a higher metabolism in the left amygdala, while the patients treated for a long period of time had a lower metabolism in the left amygdala (ANOVA F = 4.80, $P < 0.05$).

Relative metabolic rates

Relative metabolic rates of the patients were decreased in the same regions as for absolute metabolic rates (Tables 5 and 6). Relative metabolism was also decreased in the parietal areas 39 + 40. The left caudate was the only region with an increased relative metabolism. The variances of the relative values were similar in the two groups, which is to be expected since

the calculation of relative values involves a normalization of data (Tables 5 and 6). A lower relative metabolism in the left area 22 of the patients was found, while the controls had the opposite asymmetry (ANOVA F = 6.24, $P < 0.05$). A similar pattern (patients: left < right, controls: left > right) was found in Brodmann area 11 (ANOVA F = 5.18, $P < 0.05$).

The relative metabolism in the caudate was higher in the patients with more than one psychotic episode than that of the first episode patients and was lowest in the controls (ANOVA F = 3.90, $P < 0.05$). The opposite was obtained for area 32, i.e. the controls had the highest relative metabolism in this area, and the first episode patients had a slightly higher metabolism than the more chronic patients (ANOVA F = 4.20, $P < 0.05$). A higher relative metabolism of Brodmann area 23 was seen in patients under long duration of neuroleptic treatment (> 3 months) than in controls and in patients with short term (up to 3 months) treatment (ANOVA, F = 3.55, $P < 0.05$). The pattern was reversed, i.e. controls > short term treatment > = long term treatment for area 32 (ANOVA, F = 3.20, $P < 0.05$). The controls and short term treatment patients had a higher relative metabolism of the left side of the amygdala whereas the long term treatment groups had a higher relative metabolism of the right amygdala (ANOVA, F = 6.69, $P < 0.01$).

Of the diagnostic subgroups the hebephrenic patients were found to have a higher relative metabolism in area 32 than the paranoid patients. Both groups had a lower relative metabolic rate than the controls (ANOVA, F = 6.12, $P < 0.01$). In Brodmann area 6 the diagnostic subgroups had a different lateralization of metabolism: the paranoid group; right < left side, hebephrenic group; right > left and controls right > left (ANOVA, F = 3.74, $P < 0.05$). In Brodmann area 22, paranoid and hebephrenic patients had the same asymmetry: right > left, controls right < left side (ANOVA, F = 4.45, $P < 0.05$). In two further regions, amygdala and area 32, there was a tendency for a relation between groups and asymmetric metabolism. Also in these two regions the hebephrenics tended to have higher relative metabolic rates on the right side than the controls.

Table 7
Asymmetries in regional left-right glucose metabolism in healthy volunteers and drug free schizophrenic patients

Brain region	*n*	Ratios: Left/right side		
		Controls	*n*	Patients
Brodmann areas 22	10	1.05 ± 0.02*	20	0.98 ± 0.02
Caudate nucleus	10	0.95 ± 0.02*	20	1.01 ± 0.03
Amygdala	6	1.19 ± 0.06*	10	1.11 ± 0.05*

Mean ± s.e. Data represents deviations from 1.00 within the controls and the patients respectively. Two tailed t-test * $P < 0.05$.

Sex and right handedness

Male and right-handed subjects were studied separately for the regions in which differences were obtained between controls and patients (area 22, 32, 39 + 40, caudate, lentiformis both absolute and relative metabolic rates). These analyses did not change the results described above.

Asymmetries in metabolism

Besides the above reported relationships between groups and left-right asymmetries in metabolism lateralization of metabolism was analyzed by making a ratio between the metabolic rates of the left hemisphere and those of the right one. If the metabolism is equal on both sides, the ratio will be 1.00. In the controls, asymmetries were found in three regions (area 22, caudate, amygdala) and in the patients only in one (amygdala) (Table 7).

Anterior-posterior gradients

In order to look for a hypofrontal or hyperfrontal pattern of the metabolism, ratios between metabolic rates of frontal cortical areas and the temporal and parietal areas were made. The ratios of the patients were not below 1.00 in any case and were significantly higher in several instances than those of the controls

Table 8
Ratios between frontal and posterior cortical glucose metabolism in healthy volunteers and drug free schizophrenic patients

Brain region	Controls (n = 10)	Patients (n = 20)
Brodmann 6/22		
dx	1.07 ± 0.020	1.09 ± 0.036
sin	1.00 ± 0.021	1.11 ± 0.027 **
Brodmann 6/39+40		
dx	1.00 ± 0.013	1.05 ± 0.025 +
sin	0.99 ± 0.019	1.05 ± 0.018 *
Brodmann 8/22		
dx	1.08 ± 0.202	1.15 ± 0.046
sin	1.02 ± 0.030	1.13 ± 0.030 *
Brodmann 8/39+40		
dx	1.00 ± 0.021	1.11 ± 0.042 *
sin	1.01 ± 0.032	1.07 ± 0.026
Brodmann 9/22		
dx	1.06 ± 0.022	1.06 ± 0.028
sin	1.00 ± 0.017	1.10 ± 0.026 **
Brodmann 9/39+40		
dx	0.99 ± 0.021	1.03 ± 0.019
sin	0.99 ± 0.021	1.05 ± 0.027 +
Brodmann 10/22		
dx	1.05 ± 0.021	1.04 ± 0.024
sin	0.99 ± 0.013	1.05 ± 0.021 *
Brodmann 10/39+40		
dx	0.98 ± 0.018	1.00 ± 0.022
sin	0.97 ± 0.020	1.00 ± 0.017

Mean values ± s.e. In the patient group n = 19 for Brodmann 8 ratios. For comparison between controls and patients two tailed t-test was used. + $P < 0.1$; * $P < 0.05$; ** $P < 0.01$.

(Table 8). This was especially pronounced on the left side and for area 22, when compared to areas 6 and 9.

Metabolism and clinical ratings

Morbidity scores from the CPRS ratings were correlated to the metabolic values. Global, positive or depressive symptoms did not correlate to regional brain metabolism. However, autistic or negative symptoms demonstrated significant negative correlations to the metabolic rates of the regions investigated (Table 9). Thus, the more autistic the patient was, the lower the metabolism (Fig. 3). Relative metabolic data demonstrated only one significant relationship to clinical symptoms, namely positive symptoms and the relative metabolite rate of the right lentiform nucleus ($r = -0.50$, $P < 0.05$). Only in single cases, correlations between relative and absolute metabolic rates were found.

CT and metabolism

The brain ventricular index (VIX) was calculated by dividing the largest distance between the later al walls of the frontal horns with the largest inner skull diameter. There was no significant differences in the index of the patients (n = 20, 0.26 ± 0.020 (SD)) and that of the controls (n = 10, 0.25 ± 0.013 (SD)). No correlations between the indixes and the metabolic rates were found. In three patients clear cut signs of cortical atro phy were found. In patient 5, cortical atrophy was demonstrated in the entire hemisphere. Patient 6 showed signs of atrophy in the parietal areas. These two patients had the third highest and the highest metabolic rates, respectively. The third patient (no. 7) had atrophic changes of the frontal cortical areas and she had the third lowest metabolic rate.

Discussion

The cerebral metabolic rate of glucose (CMRglc) found in controls was similar to those found in PET studies of healthy volunteers with (18F) 2-deoxy-D-glucose as the tracer (29–31). The model used with ^{11}C-glucose as the tracer in-

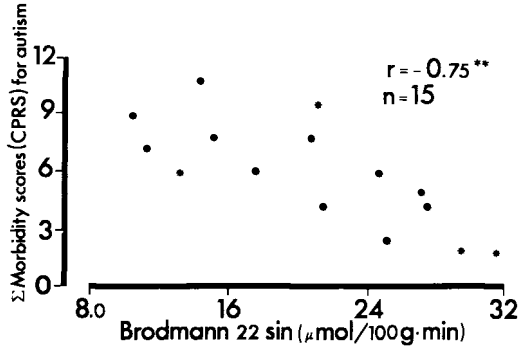

Fig. 3. Relationships between CMRglc of the superior left temporal cortex and morbidity scores for autism or negative symptoms.

Table 9
Correlation between regional brain glucose metabolism and clinical symptomatology in drug free schizophrenic patients

Brain region	Global morbidity	Subscales from the CPRS		
		Positive symptoms	Autism	Depressive symptoms
Brodmann area 9				
Right	0.06	-0.29	-0.64**	-0.-27
Left	0.03	-0.29	-0.69**	-0.25
Brodmann area 10				
Right	-0.02	-0.30	-0.69**	-0.33
Left	0.05	-0.32	-0.67**	-0.28
Brodmann area 22				
Right	0.05	-0.20	-0.68**	-0.41
Left	-0.05	-0.28	-0.75**	-0.35
Brodmann area 32				
Right	-0.01	-0.39	-0.65**	-0.43
Left	-0.03	-0.27	-0.70**	-0.25
Lentiform nucleus				
Right	-0.08	-0.34	-0.70**	-0.32
Left	-0.02	-0.36	-0.64**	-0.34

The regions were selected on the basis for alterations in metabolism or in relation to theories of brain dysfunction in schizophrenia. Product moment correlation coefficients $n = 15$; ** $P < 0.01$.

volves a correction for the egress of $^{11}C\text{-}CO_2$. This implies that the level of CMRglc is partly dependent on the cerebral blood flow (CBF). In CBF studies of schizophrenics a reduced cortical blood flow has usually been found (1, 4, 8). If this is so, then the $^{11}C\text{-}CO_2$ egress has been overestimated in the patients resulting in a correction factor of the CMRglc which is too large for the schizophrenics. Thus, if anything, the metabolic rates should be even lower in the patients. The findings of lower regional metabolic rates in schizophrenic patients than in controls are in agreement with results in two recent studies (10, 15).

The main finding of the present study was the wide variation in values of CMRglc in the schizophrenics. The rates were uniformly distributed, and therefore no basis for subgrouping the patients was obtained. The wide range of metabolic rates makes it more difficult to find mean differences between groups, implying that interpretations from patient groups that are too small might be invalid. In both the absolute and relative metabolic rates, the more posterior cortical areas and the subcortical structures seemed to be most affected. This was also supported by the calculated ratios between frontal cortical areas and parietal and temporal cortical areas respectively. However, it should be emphasized that the CMRglc of the frontal cortex of the schizophrenics tended to be lower than that of the controls, and a high proportion of the schizophrenics had metabolic rates much lower than those of the healthy volunteers.

The significance of the slightly lower metabolic rate of the left lentiform nucleus of the patients is supported by similar findings in other studies (3, 13). A functional change of the striatum in schizophrenics is of interest in relation to the dopamine hypothesis of schizophrenia. Postmortem brain findings have reported an increased number of D2 dopamine receptors in striatum of some schizophrenic patients (32). PET allows the determination of D2 dopamine receptors in the living human brain (33). However, in young drug naive schizophrenic patients, PET revealed an unchanged number of D2 dopamine receptors (34).

Interestingly, a significant asymmetry was found in the metabolic rates of the temporal lobes. The patients had a reduced metabolism in the left Brodmann area 22 corresponding to the superior temporal cortex and the area of Wer-

nicke. Similar findings were also reported by Kling et al. (11). The dysfunction of this area is of particular interest considering the coupling between psychosis and left temporal lobe epilepsy (35). The decrease in CMRglc of the frontomedial cortical area 32 is more difficult to reconcile with previous theories of schizophrenia. Brodmann area 32 is probably a transmission region between the prefrontal cortex and the limbic cortex, and it has been suggested that its function may be altered in schizophrenia.

The differences obtained in regional metabolic rates were most pronounced in patients with a subchronic or a chronic course of the illness. These patients had the widest ranges in the metabolic rates. This fact may explain some of the inconsistency of PET results in schizophrenics, since levels of mean metabolic rates in small patient groups may be highly dependent on the selection of patients. The more pronounced decrease in metabolic rates of the more chronic patients might be due to the process of the disease, since the duration of neuroleptic treatment did not explain the variance in the metabolic rates of the patients. Our data do not support the hypothesis that neuroleptic treatment should be associated with the development of so-called tardive dysmentia (36).

Clinically there are pronounced differences between paranoid and hebephrenic patients. However, there were no group differences in regional metabolic rates between the two patient categories except in area 32 where the hebephrenics had a higher relative metabolic rate. The asymmetry found in Brodmann area 22 was similar for paranoid and hebephrenic patients, i.e. a lower metabolic rate of the left side. However, with regard to the amygdala the hebephrenic patients had an asymmetry opposite to that of controls and paranoid patients. Thus, the hebephrenics had a higher metabolic rate in the right than in the left amygdala. This might explain why patients with more psychotic episodes and a longer duration of neuroleptic treatment demonstrated an asymmetry similar to the hebephrenics. Only one of the eight hebephrenic patients belonged to the group of first psychotic episode patients while six of the 10 paranoid patients were first episode. Accordingly, a higher proportion of the hebephrenics (five of eight) had a long duration of neuroleptic treatment compared to the paranoid patients (two of 10). These findings might indicate a correlation between hebephrenia and a reversed functional asymmetry of the amygdala but not to a chronic course or to long-term neuroleptic treatment. An asymmetry of the dopamine content in the amygdala in schizophrenic patients as opposed to the controls has been reported (37). The dopamine levels were increased on the left side. An increased dopamine content might indicate a reduced metabolism. To our knowledge Reynolds and coworkers have not subtyped their patients, which should indeed be of interest.

The significance of changes in metabolic rates may be validated by correlations to clinical symptoms. However, global judgement of the disease, positive or depressive symptoms were not correlated to CMRglc. Autistic or negative symptoms were however, negatively correlated to CMRglc. The correlation did not seem to be confined to any special region. Clinically, autistic or negative schizophrenics may be described as lacking psychic energy, and this was literally the finding. Similar relationships have been reported by others (1, 10).

Calculation of relative metabolic rates implies a decrease in the degree of variation, thereby increasing the possibility for finding mean group differences. Changes in relative metabolic rates were similar to those found for absolute metabolic rates, thus substantiating the divergencies found in regional metabolic rates of schizophrenic patients. Relative values may be used to identify distribution differences in regional metabolic rates and left/right assymmetries in metabolism. However, the relative level is sometimes used synonymously with the metabolic level which is obviously wrong. The calculation of relative rates means the loss of individual information. Therefore results of multivariate analyses and correlations between relative metabolic data and clinical variables should be interpreted very cautiously. The ambiguousness with relative values is illustrated by our finding of a hyperfrontal pattern in the patients. However, looking at the absolute values, the patients, if anything, had a decreased frontal metabolism. In a study

by Wolkin et al. (10), reduced frontal cortical metabolism was found in the schizophrenic patients but this difference disappeared when cortical ratios were calculated.

In conclusion, schizophrenic patients had a wide range of the CMRglc in all regions studied. Metabolic rates were negatively correlated to autistic or negative symptoms. A lower metabolism was associated with a more chronic course of the disease but not with the duration of neuroleptic treatment. A lower metabolism of the left temporal cortical region (Brodmann area 22) was found in the schizophrenics. Hebephrenics had an asymmetric metabolism of the amygdala in opposite to that of the controls and paranoid patients. By and large the results did not indicate a specific locus of abberant metabolism in the schizophrenic patients, but rather disturbances in more general mechanisms governing metabolism or neuronal function in schizophrenics (38).

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