

Positron Emission Tomography in Psychiatry

Frits-Axel Wiesel

From Department of Psychiatry and Psychology, Karolinska Institute, Stockholm, Sweden

(Received 14 November 1988)

Summary

Positron emission tomography permits the study of human brain function. With a positron labelled tracer and a model for quantitation, regional brain metabolism and neuroreceptor characteristics can be determined with PET. Schizophrenia is the most extensively studied psychiatric disorder. Most studies have demonstrated decreased metabolic rates in wide areas of the brain. It is proposed that the metabolic changes observed in the brains of schizophrenic patients are due to a fundamental change in neuronal function. Fewer studies have been performed in other psychiatric disorders. Bipolar depressed patients probably have a decreased brain metabolism. Obsessive compulsive and panic disorders (if sensitive to lactate) have an increased brain metabolism. This is probably also the case for female anorectic patients. Alcohol dependent subjects with a long duration of abuse may have a decreased brain metabolism. Neuroreceptor studies with PET have in one study of psychotropic drug naive schizophrenic patients demonstrated an increase of D₂-dopamine receptors. In another study no difference between controls and patients was found. Treatment of schizophrenic patients with conventional doses of neuroleptic drugs results in a D₂ receptor occupancy of 65 to 85 per cent, suggesting that there is no need for high dose treatment in schizophrenic patients. The studies reviewed clearly demonstrate that PET is a valuable tool in psychiatric research.

Knowledge of brain function must be an ultimate demand in neurobiological oriented psychiatry. During the last 2 decades several techniques have been introduced to research in psychiatry making it possible to study various aspects of brain function in relation to disease and treatment. The most powerful analytical technology introduced to study brain function is positron emission tomography (PET). PET is an analytical imaging technique using radioactive tracers making it possible to study regional brain biochemistry and neuroreceptor characteristics in the living human brain. Morphological imaging techniques like computed tomography (CT) and magnetic resonance (MR) have demonstrated changes in psychiatric patients, but the changes are small and seem to be unspecific. However, these

morphological changes may be the tip of an iceberg, *i.e.* reflecting a severe brain dysfunction which may be detected by positron emission tomography using suitable metabolic tracers or ligands.

So far most PET-studies in psychiatric patients have dealt with regional glucose metabolism which have increased our knowledge of brain function in psychiatric patients. A new field of application is the study of neuroreceptor characteristics and thereby also mechanisms of action of psychotropic drugs, which seems even more promising.

Positron camera

The word positron comes out of the use of positron emitting radioisotopes in the investigations. Positrons (positively charged electrons) are emitted from the nucleus of the radioisotope and will travel about 2 mm in the tissue whereafter they will interact with an electron¹. These 2 particles will undergo annihilation and their mass is converted into 2 high energy photons (511 keW) travelling 180° from each other. The level of energy makes it possible to use an external detection system—the positron camera. The radioisotopes used in man are ¹¹C, ¹³N, ¹⁵O, ¹⁸F with short half lives of 20 min, 10 min, 2 min and 110 min respectively. This means that the isotopes must be produced nearby the positron camera and very high demands are put on radiochemistry *i.e.* rapid synthesis with high specific activity, identification and pharmaceutical sterile compounds for the injection². The image forming process in PET has 3 principal steps. The detection of the gamma rays emitted in the positron-annihilation process, the identification of the direction of the radioactivity and the reconstruction of the distribution of radiation into an accurate geometric image³. These demands are realized by placing scintillation detectors for coincidence detection of radioactivity in rings around the head of the subject. The distribution of radioactivity is imaged by sophisticated computer technology. The technique is very complex but to be more comprehensible one can say, that in principle PET is autoradiography *in vivo*.

Physiological Studies

The radioactivity data collected by the positron camera after the i.v. injection of a metabolic tracer must be processed according to a model for the biochemical process under investigation to be functionally meaningful. Quantitative data can be obtained for brain blood volume, blood flow, oxygen and glucose consumption, transport of tracers across the blood-brain barrier and possible also for the study of protein synthesis in the brain⁴.

Brain glucose metabolism

Regional brain glucose metabolism is of great interest since neuronal activity is probably directly related to the glucose consumption^{5, 6}. Thus, by determining metabolic rates one can investigate if the symptomatology of different categories of psychiatric patients can be traced to changes in neuronal function and thereby increase our understanding of the psychiatric diseases and improve our diagnostic work and the treatment of our patients. Sokoloff and coworkers have developed a method for calculating regional glucose metabolism by the use of radiolabelled 2-deoxyglucose (DG) (for review see reference 7). Glucose and 2-deoxyglucose are competitive substrates since they use the same carrier across the blood-brain barrier and are phosphorylated by the same enzyme hexokinase to glucose-6-phosphate (G-6-P) and 2-deoxyglucose-6-phosphate (DG-6-P). However, unlike G-6-P, DG-6-P is in principle not further metabolized but trapped in the tissue. DG can be labelled with a positron emitting isotope and injected into a human and it has been shown, that the accumulation of radioactivity adapted to a 3 compartment model (tracer in plasma and tissue, metabolized tracer in tissue) equals regional brain glucose metabolism⁸. In this calculation one has to use a constant, the lumped constant, which combines 6 other constants related to enzyme kinetics and the distribution of glucose and deoxyglucose⁷. This constant differs among species. By labelling deoxyglucose with ¹⁸F (or ¹¹C) it is possible to study regional brain glucose metabolism in the living human brain and several aspects of brain function can be studied⁹. However, it should be observed, that the metabolic level may not always be comparable among studies since different lumped constants may have been used. The level of the lumped constant will directly influence the metabolic level. The lumped constant initially used was estimated as 0.42, but is probably too low, since determinations in man have given values of 0.52 for ¹⁸F-DG, and 0.56 for ¹¹C-DG¹⁰. Thus the metabolic rate will be overestimated with 20–25 per cent if the lower value of 0.42 is used for the lumped constant.

Brain glucose metabolism in man has also been calculated according to a model for ¹¹C-glucose¹¹. The advantage with ¹¹C-glucose as the tracer is the fact that glucose is the natural substrate for the brain. The drawback is that radiolabelled glucose is not trapped in the tissue, but will be further metabolized mainly to ¹¹C-CO₂. However, this is compensated for by the model (uniformly labelled and ¹¹C-1-glucose give almost identical metabolic rates, personal communication, Blomqvist). Using ¹¹C-glucose as the tracer, brain glucose metabolism may be underestimated with 20 per cent assuming that the lumped constant for ¹¹C-DG is correctly determined in man.

Oxygen metabolism and blood flow

Oxygen metabolism and blood flow can be determined with the use of $O^{15}O$ (inhaled) and $H_2^{15}O$ (injection) as tracers respectively¹². The short half life of ^{15}O (2 min) makes it possible to perform multiple sequential studies in the same subject to study the effect of different physiological stimuli. On the other hand, since the investigation cannot exceed 1 min there can be difficulties in obtaining steady state for the physiological stimulation under investigation.

In the calculation of oxygen metabolism, a model consisting of 2 compartments is used, corresponding to the different molecular forms of ^{15}O namely $O^{15}O$ and $H_2^{15}O$ found in the brain¹³. One has also to measure the blood volume which can be occupied by $C^{15}O$ or ^{11}CO , inhaled and injected respectively (^{11}CO is bound to the haemoglobin of the patient's own blood corpuscles which are injected). Determination of the blood volume is essential to determine the concentration of the radioactive isotope in the vascular compartment as compared to the extravascular compartment of the brain. Blood flow must also be determined if oxygen metabolism is to be calculated. $CMRO_2$ is calculated as the product of the local extraction of oxygen, the local blood flow and the arterial oxygen content¹². Thus several investigations must be made in a subject, but the simplicity of the model is an advantage.

Pitfalls in the determination of metabolic rates

The critical point in the determination of brain metabolism is the model used. However, several other factors must also be considered in the evaluation of the validity of the results. The accuracy in the determination of regional metabolic rate is influenced by the resolution of the PET camera (full width at half maximum, FWHM). The resolution determines the minimum size of the objects that can be studied with the camera¹⁴. In addition to the size of a region, the shape also has to be considered both in the drawings and in the interpretation of the metabolic value. The smallest errors occur in large circular structures surrounded by regions of similar pixel values. The so-called partial volume effect is related to the structure, the size and the shape of the region¹⁴. Obviously many PET cameras used so far have such low resolutions that important questions in relation to psychiatric diseases cannot be investigated. The new generation of cameras have a resolution of 3 to 5 mm, which will make it possible to study small structures in the limbic system, thalamus and the brainstem that may give vital information in relation to psychiatric disorders. In determining the metabolic rate in a region, another prerequisite is that the region is correctly delineated. The most accurate way to define the region of interest is from CT or MR images of the subject's own brain. The defined regions of interest are then transferred to the corresponding PET image and the amount of radioactivity can be

determined. This method is time consuming, and explains why several automated techniques have been developed to allow a rapid delineation of the regions of interest. The accuracy of these techniques is completely dependent on how carefully the anatomy of the individual brain is taken into account in the automated drawings. In psychiatric research it is of interest to study differences in function between left and right hemispheres. However, differences between the 2 hemispheres can very easily be caused by small tiltings in one of the planes, which is why left/right differences should be interpreted with care. Another factor, that probably influences metabolic rates, is the condition of the subject during the investigation. A resting condition comprises either a patient in a room with damped noise and lights, with the eyes opened and no ear plugs, or else a patient with eyes covered and ears plugged. How much such differences between investigation conditions influence the results is not known, nor if differences in unrestrained mental activity influence regional metabolism differently. To overcome these problems some investigators have used some kind of stimulation during the investigation so that both the volunteers and the patients will be occupied with a similar task or stimuli and therefore hopefully have the same level of attention or mental activity. However, the task or stimuli must be correctly chosen in relation to the dysfunction being investigated (which can only be hypothesized), otherwise the stimuli may rather blur the picture.

The reason for determining glucose metabolism is its close relationship to the neuronal activity of the brain^{5, 6}. However, the correctness of this approach for stimulation studies has been questioned. Thus peripheral tactile stimulation increased oxygen metabolism by only 5 per cent, despite a large increase in local cerebral blood flow (29 per cent)¹⁵. In another study Fox and coworkers¹⁶ determined oxygen metabolism, glucose metabolism and blood flow before and after visual stimulation. Blood flow and glucose uptake increased by 50 per cent, but the oxygen consumption by only 5 per cent following stimulation. These findings must be replicated, but they may imply that glucose metabolic rates should be determined during the resting condition, since stimulation may only increase glucose uptake for purposes other than oxidation.

Neuroreceptors

PET is in principle autoradiography *in vivo*. Visualization of receptor distribution and receptor characteristics using approaches similar to autoradiography *in vitro* should be possible¹⁷. However, special demands must be considered when developing radiolabelled ligands for PET¹⁸. There is no possibility for getting rid of nonspecific binding, and so the ratio of total to nonspecific binding must be reasonably high within a short period of time. The use of short-lived positron emitting isotopes puts special demands on radiochemistry such as rapid synthesis and

Table 1. Regional cerebral glucose metabolism ($\mu\text{mol}/100 \text{ g} \times \text{min}$) in schizophrenic patients

| Regions | n | Controls | | | Patients | | | Setting | Ref. |
|--|----|--------------------|--------------------|--------------------|----------|-------------------------|-------------------------|-------------------------|---|
| | | Left | Both sides | Right | n | Left | Both sides | Right | |
| Frontal cortex ⁽¹⁾ | 19 | 29.2±8.3 | 29.2±8.3 | 29.2±8.3 | 16 | 32.9±7.1 | 32.9±7.1 | 32.9±7.1 | 37 |
| Posterior cortex | 19 | 26.5±7.6 | 26.5±7.6 | 26.5±7.6 | 16 | 31.9±7.9* | 31.9±7.9* | 31.9±7.9* | 38 |
| Frontal cortex ⁽²⁾ | 24 | 22.8 | 22.5 | 22.8 | 21 | 24.9 | 24.6 | 24.6 | El. stim right arm $^{18}\text{F}-\text{DG}$ 17.5 mm |
| Caudate nucleus | 24 | 17.1 | 17.2 | 17.1 | 21 | 19.9 | 20.5 | 20.5 | El. stim right arm $^{18}\text{F}-\text{DG}$ 17.5 mm |
| Putamen | 24 | 22.9 | 22.5 | 22.9 | 21 | 25.5 | 25.5 | 25.5 | 38 |
| Globus pallidus | 24 | 21.9 | 21.0 | 21.9 | 21 | 23.4 | 23.4 | 23.4 | 38 |
| Frontal brain ⁽³⁾ | 11 | 20.6±2.9 | 20.6±2.9 | 20.6±2.9 | 13 | 17.5±4.8 ⁽³⁾ | 17.5±4.8 ⁽³⁾ | 17.5±4.8 ⁽³⁾ | 49 |
| Posterior brain | 11 | 18.1±2.8 | 18.1±2.8 | 18.1±2.8 | 13 | 16.4±4.6 ⁽³⁾ | 16.4±4.6 ⁽³⁾ | 16.4±4.6 ⁽³⁾ | 49 |
| Frontal cortex | 12 | 22.4±3.4 | 22.1±3.4 | 22.4±3.4 | 12 | 18.4±2.9 ⁽⁴⁾ | 18.4±2.7 ⁽⁴⁾ | 18.4±2.7 ⁽⁴⁾ | 45 |
| Parietal cortex | 12 | 19.2±4.1 | 19.7±4.1 | 19.2±4.1 | 12 | 15.9±2.6 ⁽⁴⁾ | 16.3±2.6 ⁽⁴⁾ | 16.3±2.6 ⁽⁴⁾ | 45 |
| Temporal cortex | 12 | 20.1±3.4 | 20.2±3.3 | 20.1±3.4 | 12 | 17.0±3.3 ⁽⁴⁾ | 16.6±2.2 ⁽⁴⁾ | 16.6±2.2 ⁽⁴⁾ | 45 |
| Whole cortex ⁽⁵⁾ | 18 | 21.9±3.9 | 21.8±3.7 | 21.9±3.9 | 20 | 18.7±3.9** | 18.6±3.8** | 18.6±3.8** | 35 |
| Caudate nucleus | 18 | 22.2±4.1 | 21.3±3.7 | 22.2±4.1 | 20 | 18.8±4.1* | 18.3±3.7* | 18.3±3.7* | 35 |
| Lentiform nucleus | 18 | 24.4±4.5 | 23.9±4.4 | 24.4±4.5 | 20 | 22.4±4.9 | 21.9±4.7 | 21.9±4.7 | 35 |
| Prefrontal cortex ⁽⁶⁾ (area 9) | 9 | 25.5±2.5 | 26.0±2.6 | 25.5±2.5 | 15 | 23.1±7.6 | 23.2±7.5 | 23.2±7.5 | 36 |
| Medial frontal cortex (area 32) | 9 | 27.5±2.4 | 26.5±3.0 | 27.5±2.4 | 15 | 22.7±7.3* | 22.4±6.2* | 22.4±6.2* | 36 |
| Sup temp cortex (area 22) | 9 | 25.8±2.9 | 24.6±2.9 | 25.8±2.9 | 15 | 20.8±6.9* | 21.3±6.6 | 21.3±6.6 | 36 |
| Parietal cortex (area 39+40) | 9 | 26.3±2.3 | 26.2±3.1 | 26.3±2.3 | 15 | 22.8±7.8 | 22.7±7.5 | 22.7±7.5 | 36 |
| Caudate nucleus | 9 | 20.5±1.6 | 21.8±2.0 | 20.5±1.6 | 15 | 19.5±5.8 | 19.4±6.8 | 19.4±6.8 | 36 |
| Lentiform nucleus | 9 | 25.8±2.9 | 25.9±4.0 | 25.8±2.9 | 15 | 21.5±7.0* | 21.6±7.5 | 21.6±7.5 | 36 |
| Frontal cortex ⁽⁷⁾ | 8 | 36.6±1.3 (s.e.) | 35.3±1.2 (s.e.) | 36.6±1.3 (s.e.) | 10 | 29.8±1.4** (s.e.) | 30.9±1.5* (s.e.) | 30.9±1.5* (s.e.) | 43 |

| | | | | | | | | |
|-------------------------------|----|----------------------------------|----------------------------------|----|--|--|--|---------|
| Temporal cortex | 8 | 35.1 ± 1.5 (s.e.) | 35.0 ± 1.1 (s.e.) | 10 | $29.3 \pm 1.0^{**}$ (s.e.) | $30.5 \pm 1.2^*$ (s.e.) | $^{18}\text{F}-\text{DG}$ | 11.8 mm |
| Caudate nucleus | 8 | 34.0 ± 1.5 (s.e.) | 30.3 ± 1.7 (s.e.) | 10 | 33.0 ± 1.8 (s.e.) | 29.9 ± 1.5 (s.e.) | $^{18}\text{F}-\text{DG}$ | 11.8 mm |
| Lentiform nucleus | 8 | 40.7 ± 1.2 (s.e.) | 36.6 ± 1.6 (s.e.) | 10 | 37.7 ± 1.1 (s.e.) | 36.3 ± 1.3 (s.e.) | $^{18}\text{F}-\text{DG}$ | 11.8 mm |
| Frontal brain ⁽⁸⁾ | 8 | 40.9 ± 5.9 37.8 ± 3.9 | 40.9 ± 5.5 37.1 ± 4.0 | 13 | $34.2 \pm 5.2^{**}$ $32.8 \pm 3.0^{**}$ | $34.0 \pm 4.8^{**}$ $32.7 \pm 3.2^{**}$ | Rest. cond. $^{18}\text{F}-\text{DG}$ | 11.8 mm |
| Posterior brain | 8 | | | | | | | |
| Frontal cortex ⁽⁹⁾ | 12 | 40.3 ± 3.0 | 40.0 ± 2.8 | 18 | $35.2 \pm 5.5^{**}$ | $35.4 \pm 5.3^{**}$ | Rest. cond. $^{11}\text{C}-\text{DG}$ | 11.8 mm |
| Parietal cortex | 12 | 38.6 ± 3.6 | 38.5 ± 2.7 | 18 | 35.3 ± 5.3 | $35.0 \pm 4.7^*$ | | |
| Temporal cortex | 12 | 37.3 ± 3.1 | 37.5 ± 2.5 | 18 | 34.0 ± 5.3 | $34.0 \pm 4.7^*$ | | |

Mean \pm SD and two tailed Student's t-test if not indicated otherwise. Regions were selected to favour comparisons among groups. Several authors have published their results successively and the cited reference is meant to be the one with the highest number of subjects investigated. Patients were not treated with neuroleptics if not stated otherwise.

- (1) Supraventricular slice, hemisphere differences: controls' higher left activity than patients' ($p < 0.01$).
- (2) Slice through the basal ganglia area, no hemisphere differences between controls and patients (only means were presented).
- (3) Slice through the basal ganglia area. There was a difference between controls and patients in the adjusted mean of frontal brain metabolism, controls 2.6 $\mu\text{mol}/100 \text{ g} \cdot \text{min} >$ patients ($p < 0.01$).
- (4) ANOVA: normals had higher metabolism than patients ($p < 0.05$). Patients with high BPRS scores were associated with higher left hemisphere metabolic rates than in patients with low BPRS scores ($p < 0.025$).
- (5) * $p < 0.05$, ** $p < 0.01$.
- (6) * $p < 0.05$. The mean metabolic rate in left Brodmann area 22 was lower in patients than controls (ANOVA, hemisphere interaction $p < 0.05$).
- (7) Midventricular slice, * $p < 0.05$, ** $p < 0.01$.
- (8) Midventricular slice, Bonferroni (t-test), ** $p < 0.01$.
- (9) * $p < 0.05$, ** $p < 0.01$.

high specific activity of the radiolabelled ligand. Other demands on ligands useful for PET are high selectivity and stereoselectivity, nanomolar binding affinity for the receptor, rapid establishment for steady state over the blood-brain barrier, and the metabolism of the ligand must be known, as well as a low degree of nonspecific binding *in vivo*¹⁸. Kumar and coworkers¹⁹ were the first to use a radiolabelled ligand, ¹¹C flunitrazepam, for pharmacological studies with PET. A major breakthrough in psychopharmacology research has been the possibility of characterizing neuro-receptors *in vivo* with PET, *i.e.* to determine receptor numbers (B_{max}) and the dissociation constant (K_d). Several models have been presented. The weakness and the strength of these models are discussed by Huang and coworkers²⁰, see also Swart and Korf²¹. Two models have been successfully applied to determine D₂-dopamine receptor numbers in man. Wong and coworkers^{22, 23} have used a 3 compartment model in which the rate constant of 3-N-(¹¹C)-methylspiperone (binds to both D₂ and serotonin-2 receptors) binding (k_3) to the D₂ receptor is determined without and after an oral dose of haloperidol, permitting one to calculate B_{max} and K_d . Farde and coworkers²⁴ have used basic concepts from receptor pharmacology in their model. Thus, saturation analysis of ¹¹C-raclopride (a selective D₂-receptor antagonist) is used to determine D₂-receptor numbers. Several PET experiments are performed with different specific activities of ¹¹C-raclopride, *i.e.* the fraction of labelled to unlabelled ligand will vary among the PET experiments (the increasing amounts of unlabelled ligand will saturate the receptors). Under the assumption of equilibrium B_{max} - and K_d -values could be determined from the saturation curve or the Scatchard plot. In both models cerebellum is used to estimate free drug concentration. The saturation analysis has also been applied successfully to determine benzodiazepine receptors in man with the ligand ¹¹C-flumazenil, a benzodiazepine receptor antagonist²⁵. Several ligands have been developed making it possible to study the receptor distribution of serotonin-2 receptors^{26, 27}, D₁-dopamine receptors²⁸, opiate receptors²⁹, muscarinic receptors³⁰, dopamine reuptake sites³¹ and dopaminergic terminals by ¹⁸F-L-DOPA³². The importance of imaging receptor distribution in man has been demonstrated by Farde *et al.*³³ who did not find any evidence of D₂-dopamine receptors in human frontal cortex as suggested from animal studies.

Hypotheses of disturbances in specific neuronal systems and psychiatric disorders will be feasible to test *in vivo* as well as mechanisms of action of psychotropic drugs.

Regional Metabolic Rates in Patients

As pointed out above, there are several pitfalls when comparing results among studies. Absolute metabolic rates are to be preferred since these rates are comprehensible from a functional point of view. However, relative rates (the regional rate versus a defined denominator for the metabolism) are more often

reported probably since less demands have to be put on the prerequisites for applying the model in the calculations. The influence of the lumped constant is eliminated³⁴ and arterialized blood instead of arterial blood can be used in the calculations^{8, 61}. Problems related to partial volume effects and the determination of regions of interest are not overcome by relative rates. However, most important defect is the loss of coupling between metabolism and neuronal function. For instance similar elevated regional relative rates will have different absolute levels if the denominator for the 2 regions are not identical. This is made even more complicated by the use of different parts of the brain as the denominator in the calculation of the relative rates among the groups. Thus some workers use the whole brain, others the ipsilateral hemisphere, the whole slice or only the ipsilateral slice in which the region is identified. Obviously the functional meaning of the relative rates must be interpreted very cautiously.

Schizophrenia

Schizophrenia is the psychiatric disorder most extensively studied with PET. By and large the results demonstrate that schizophrenic patients have reduced metabolic rates in both frontal and posterior cortical regions (Table 1). Subcortical regions seem to be less changed than cortical areas even though reduced metabolism has been reported in the caudate nucleus³⁵ and lentiform nucleus³⁶ by some investigators. Only one group has reported increased metabolic rates in schizophrenics, reaching significance in the posterior cortex (Table 1)³⁷. In a later report no differences were found (Table 1,³⁸). This discrepancy with respect to the results of other groups may be due to different settings during the investigations. Buchsbaum *et al.*^{37, 38} applied a painful electrical stimulus to the right forearm during the investigation. It is possible that this stimulus may have blurred rather than revealed differences between controls and patients.

It is striking to note that the changes in metabolic rates are not confined to any specific part of the brain (Table 1). It may indicate that schizophrenic patients suffer from a more general dysfunction in the neuronal network influencing most brain regions. By studying relationships among regional metabolic rates in patients and healthy volunteers, distinctly different patterns emerged³⁹. In the patients all regions were highly intercorrelated as if the activity among regions were synchronized (Figures 1 and 2). In controls the neocortical regions were intercorrelated (association areas), but the limbic cortical regions were not correlated to other parts of the brain (Figures 1 and 2). It is possible that some kind of a fundamental principle in neuronal function is disturbed. Schizophrenia not only involves changes in wide areas of brain function, but also peripheral manifestations of the disease are present. For instance neuromuscular abnormalities have been found in schizophrenic patients^{40, 41} and a decreased tyrosine transport in fibroblasts from schizophrenic

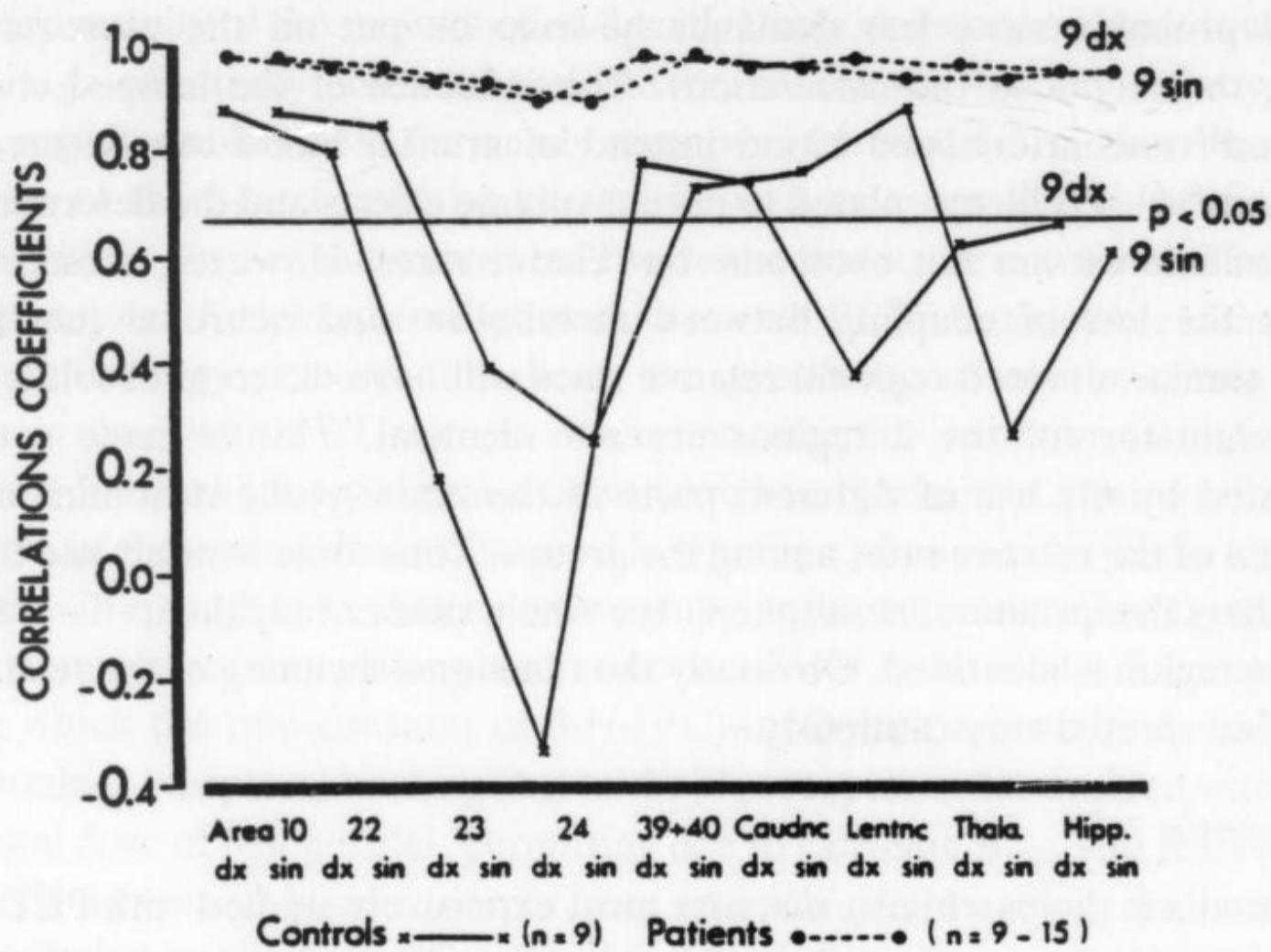


Fig. 1. Correlations between the metabolic rate of the Brodmann area 9 and the rates of 9 other brain regions, left and right side. On the y-axis is the level of the correlation coefficient (Pearson's product moment correlation) indicated. Each point and hatch indicate the correlation between Brodmann 9 (right of left side) and another brain region. The level of significance is indicated by the line followed by $p < 0.05$.

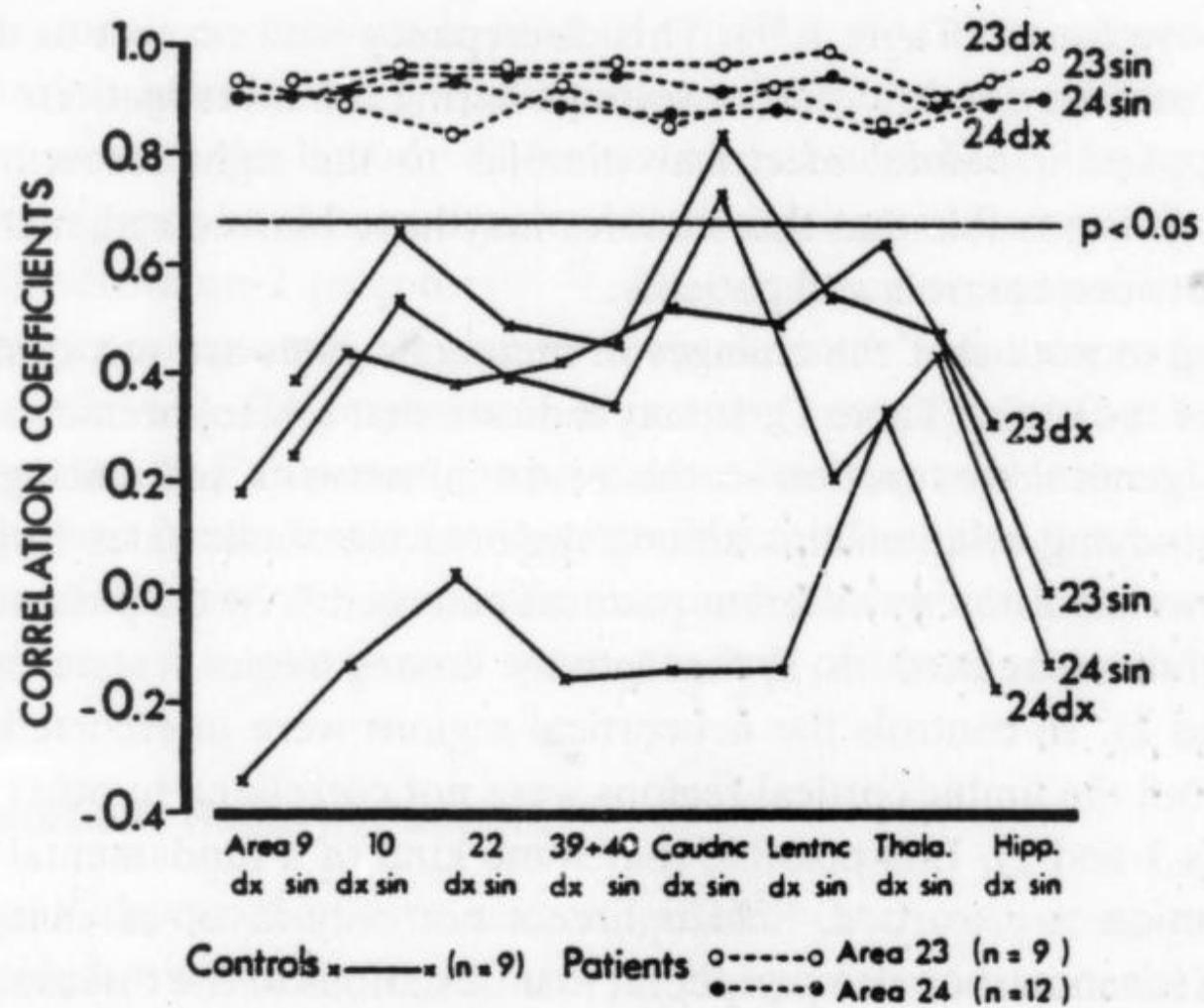


Fig. 2. Correlations between the metabolic rates of Brodmann areas 23 and 24 and the rates of 8 other brain regions, left and right side, see also Fig. 1.

patients has been observed⁴². These changes suggest a cell membrane dysfunction in schizophrenic patients. The metabolic changes observed in the brains of schizophrenics may therefore be due to a more general change in the cell membrane influencing cell function. Such a change may influence the function of the cell differently depending on the sensitivity of the specialized cell (the neuron, the muscle cell and so on) to the proposed change in the membrane.

The changes in metabolic rates observed in the patients seem to be coupled to the clinical symptomatology. Thus Wolkin *et al.*⁴³ and Wiesel *et al.*³⁶ reported that low metabolic rates were correlated to autistic or negative symptoms. Volkov *et al.*⁴⁴ demonstrated that schizophrenics with a negative symptomatology had lower metabolic rates than schizophrenics with positive symptoms. This is also supported by the finding of Gur *et al.*⁴⁵, demonstrating that high BPRS-scores were coupled to higher metabolic rates in the patients.

The significance of left/right differences in metabolism between controls and patients is far from clear. Regions both in the right and the left hemisphere demonstrated changes in the metabolism between the groups without a distinct pattern (Table 1). The fact that some comparisons were significant and others not, despite similar means, is probably due to insensitivity of the tests in detecting differences between groups (too few subjects and/or too great a variance).

Relative rates

The concept of hypofrontality in schizophrenia comes from the findings of Ingvar and Franzen⁴⁶ demonstrating that schizophrenic patients had a lower blood flow in the frontal part of the brain relative to the posterior part in contrast to the controls. However, this pattern was evident only in a group of older schizophrenic patients (mean age 61 years) and not in younger patients. Thus the findings of Sheppard *et al.*⁴⁷ and Wiesel *et al.*³⁶, who were unable to detect hypofrontality in young never drug-treated schizophrenic patients, do not contradict the early results reported by Ingvar and Franzen⁴⁶. In chronic patients hypofrontality has been found in several studies⁴⁸⁻⁵¹ but not in other studies even if the same group had performed the study^{36, 37, 43, 45, 47, 52}. Obviously hypofrontality is not a pathognomonic finding for schizophrenia, but relative rates, like absolute rates, support the view that the function of wide brain areas is involved in schizophrenia.

For subcortical areas several investigators have reported increased relative rates (Table 2)^{35, 43, 53}. Whether this indicates that the changes found in the metabolism of schizophrenic patients involve the function of the subcortical areas to a lesser degree than the cortical areas, or point to a primary disturbance of the basal ganglia area⁵³, cannot be determined. Buchsbaum and coworkers^{38, 48} and Sheppard and co-workers⁴⁷ found lower relative rates in subcortical structures. However, this may be related to the inclusion of ventricular spaces in their definitions of the regions and

Table 2. Regional cerebral relative metabolic rates in schizophrenic patients

| Regions | n | Controls | | | Patients | | | Setting | | | |
|---|----|------------|-------------|-----------|----------|-------------|--------------|-----------|---|---------------------|--------|
| | | Left | Both sides | Right | n | Left | Both sides | Right | Tracer | FWHM | Ref. |
| Frontal cortex ⁽¹⁾ | 6 | 1.02 | 1.125±0.052 | 1.00 | 8 | 0.95 | 1.064±0.041* | 0.97 | Rest. cond. ¹⁸ F-DG | 17.5 mm | 48 |
| Central grey matter ⁽²⁾ | 6 | | | | | | | | | | |
| Frontal cortex ⁽³⁾ | 19 | 1.15 | 1.15±0.08 | 1.14±0.08 | 16 | 1.12 | 1.11±0.07 | 1.09±0.07 | El. stim. right arm ¹⁸ F-DG | 17.5 mm | 37 |
| Frontal cortex ⁽⁴⁾ | 24 | 1.27 | | | 21 | 1.24 | | | | | |
| Caudate nucleus ⁽⁵⁾ | 24 | 1.07 | | | 21 | 0.96* | | | | | |
| Putamen ⁽⁵⁾ | 24 | 1.29 | | | 21 | 1.15 | | | | | |
| Globus pallidus ⁽⁴⁾ | 24 | 1.21 | | | 21 | 1.15 | | | | | |
| Anterior/posterior cortex ⁽⁶⁾ | 21 | | 1.11±0.1 | | 21 | | 1.04±0.09* | | | | |
| Globus pallidus ⁽⁷⁾ | 20 | 1.08 | | | 10 | 1.19 | | | | | |
| Prefrontal cortex ⁽⁸⁾ | 6 | 1.01±0.038 | | | | | | | | | |
| Temporal cortex | 6 | 1.02±0.045 | | | | | | | | | |
| High frontal cortex ⁽⁹⁾ | 6 | 1.01±0.04 | | | 6 | 0.96±0.05** | | | 0.92±0.07** Rest. cond. ¹⁸ F-DG | 12 mm | 55 |
| Post. inf. cortex | 6 | 1.04±0.04 | | | 6 | 1.00±0.07** | | | 0.98±0.03** Rest. cond. ¹⁸ F-DG | 8 mm | 87 |
| Post. sup. temp. cortex | 6 | 1.06±0.03 | | | 6 | 1.02±0.09** | | | 1.02±0.07 | | |
| Caudate nucleus | 6 | 0.92±0.11 | | | 6 | 1.00±0.13 | | | 1.05±0.08 | | |
| Caudate nucleus ⁽¹⁰⁾ | 18 | 1.02±0.10 | | | 20 | 1.01±0.10 | | | 0.99±0.08 Rest. cond. ¹⁸ F-DG | 16.5 mm | 35 |
| Lentiform nucleus | 18 | 1.12±0.13 | | | 20 | 1.21±0.12* | | | 1.19±0.13* | | |
| Thalamus | 18 | 1.02±0.11 | | | 20 | 1.08±0.10 | | | 1.10±0.09* | | |
| Front./post. cortex ⁽¹¹⁾ | 12 | 1.0 | | | 1.1 | 1.0 | 1.0 | 1.0 | Rest. cond. ^{O¹⁵O, CO¹⁵O} | 11 mm | 47 |
| Front.post. cortex ⁽¹²⁾ | 10 | | 1.06±0.10 | | 5 | | 1.31±0.14* | | Rest. cond. ¹⁸ F-DG | 8 mm | 52 |
| Prefrontal cortex ⁽¹³⁾ (area 9) | 10 | 1.15±0.06 | | | 12 | | 1.24±0.18* | | Rest. cond. | | 36 |
| Sup. temp. cortex (area 22) | 10 | 1.15±0.05 | | | 20 | 1.16±0.09 | | | 1.14±0.06 | | |
| | | | | | 20 | 1.06±0.08** | | | 1.09±0.10 | ¹¹ C-glu | 7.6 mm |

| | | | | | | |
|------------------------------------|----|---------------------|---------------------|----|---------------------|--|
| (area 22) | | | | | | |
| Med. front. cortex (area 32) | 10 | 1.22±0.04 | 1.18±0.10 | 20 | 1.12±0.09*** | 1.16±0.09 |
| Parietal cortex (areas 39+40) | 10 | 1.16±0.06 | 1.17±0.06 | 20 | 1.11±0.07 | 1.12±0.07* |
| Caudate nucleus | 10 | 0.91±0.05 | 0.95±0.03 | 20 | 1.00±0.10** | 0.99±1.00 |
| Lentiform nucleus | 10 | 1.13±0.06 | 1.13±0.11 | 20 | 1.08±0.07 | 1.08±0.08 |
| Area 6/39+40 | 10 | 0.99±0.02 | 1.00±0.01 | 20 | 1.05±0.02* | 1.05±0.03 |
| Front./post. brain ⁽¹⁴⁾ | 8 | 1.09 (1.02–1.14) | 1.09 (1.05–1.12) | 10 | 1.00 (0.82–1.30) | 1.04 (0.84–1.30) |
| Caudate nucleus | 8 | 1.04 (0.87–1.18) | 0.92 (0.79–1.07) | 10 | 1.14 (0.93–1.35) | 1.02 (0.80–1.21) |
| Lentiform nucleus | 8 | 1.24 (1.02–1.31) | 1.11 (0.99–1.22) | 10 | 1.28 (1.16–1.39) | 1.25 (1.06–1.42)* |
| Front. post. brain ⁽¹⁵⁾ | 8 | 1.12±0.07 | 1.10±0.06 | 13 | 1.04±0.07* | 1.04±0.06* Rest. cond. ¹⁸ F-DG 11.8 mm |
| | | | | | | 51 |
| | | | | | | 43 |

Mean ± SD, for explanation of presented data see Table 1.

- (1) Supraventricular slice level. Relative rates in relation to the slice of the region. ANOVA showed an anterior-posterior effect. No hemisphere differences between normals and patients.
 - (2) Relative rates in relation to the slices of the region. The left side tended to be lower in the patients.
 - (3) Supraventricular slice level. Relative rates in relation to the slice of the region. Normals had a higher activity in left hemisphere than the patients ($p<0.01$).
 - (4) Intraventricular slice (through the basal ganglia area). Relative rates in relation to the slice of the region.
 - (5) Midventricular slice (through the basal ganglia area). * $p<0.05$.
 - (6) Supraventricular slice (through centrum semiovale). No hemisphere differences between controls and patients.
 - (7) Globus pallidus versus whole brain. The blood flow was determined.
 - (8) Region versus the cortical rim of the ipsilateral hemisphere.
 - (9) Region versus all regions, significances are given without adjustments for the number of comparisons.
 - (10) Region versus ipsilateral cortex.
 - (11) Supraventricular slice level, basal ganglia data showed lower relative metabolism in the patients who also had less asymmetries in metabolism than the controls.
 - (12) Midcallosal slice level. The patients were on neuroleptics when investigated. One group had been on medication in one year ($n = 5$), another group ($n = 12$) in average 7.4 years. Both patients and controls showed a symmetric distribution of glucose metabolism except in corpus striatum (left>right ANOVA $p<0.01$) and superior temporal cortex (left<right).
 - (13) Region versus whole brain. ANOVA demonstrated a lower relative metabolism in left superior temporal cortex (area 22) of the patients in comparison with the controls ($p<0.05$).
 - (14) Midventricular slice level. The region versus the slice of the region, Left/right ratios in frontal cortical areas and lentiform nucleus were higher in controls than patients ($p<0.05$), * $p<0.05$ Mann-Whitney U test).
 - (15) Midventricular slice level, * $p<0.05$.
- Gur *et al.* (45) (see Table 1) didn't find any differences in anterior/posterior ratios between controls and patients. This was also the case in the study of Jernigan *et al.* (87).

the resolution of the cameras used. However, Wiesel and coworkers³⁶ found similar tendencies with lower rates in the lentiform nucleus of the patients using a camera with a relative high resolution (7.6 mm) and a more optimal delineation of the regions. A factor analysis by Volkov *et al.*⁵⁴ demonstrated that frontal relative rates were lower in patients than in the controls, with a reversed finding for subcortical rates.

It is possible that the basal ganglia have to be analysed in more detail with a high resolution camera before any firm conclusions can be drawn regarding the involvement of the basal ganglia in schizophrenia. It is also possible that the calculation of relative rates could to some extent explain the discrepancies in the results of the studies. By and large the relative rates in the patients indicate that neocortical areas are more affected than subcortical areas.

The left/right differences found do not give any clear support to the suggestion that schizophrenic patients suffer from a left hemisphere dysfunction. The results nevertheless indicate differences in hemisphere function between controls and patients since the patients appear to have fewer asymmetries than the controls. Healthy volunteers appear to have a higher metabolism in the left hemisphere relatively to the right^{36, 37, 43, 51} except in the study of Sheppard and coworkers⁴⁷. They found higher ratios for the blood flow of the right with respect to the left hemisphere in the controls, but in accordance with the other investigators, the patients had fewer asymmetries than the controls. The relative decrease of the metabolism in the left superior temporal lobe found by Wiesel and coworkers³⁶ and Kling and coworkers⁵⁵ is interesting in relation to the coupling between left temporal lobe epilepsy and psychosis.

Effects of neuroleptics on regional glucose metabolism

The most consistent pharmacological effect of neuroleptics is a blockade of D₂-dopamine receptors^{56, 57}. In the human brain D₂-dopamine receptors are concentrated in the basal ganglia³³. Neuroleptic treatment should therefore in the first place influence neuronal activity in this area and thereby possibly metabolic rates. Most neuroleptics interact with other central receptors as well, and so effects in other brain regions should also be expected. However, the studies performed so far which have aimed to investigate effects of neuroleptic treatment on glucose metabolism have not given clear-cut results. Increases in metabolism^{43, 58} as well as no change in metabolism^{59, 60} have been reported. In a recent study Wik and coworkers⁶¹ found an increase in the metabolism of the right lentiform nucleus following sulpiride treatment whereas chlorpromazine treatment did not change the metabolism. In a re-evaluation of the results from the study of DeLisi and coworkers⁵⁸, Buchsbaum and coworkers³⁸ did not find any significant changes in cortical metabolism following neuroleptic treatment. However, neuroleptic

treatment seemed to increase the metabolism in the right basal ganglia, mainly in the right putamen (although this effect was not confirmed by t-test). These findings indicate that neuroleptics increase the metabolism in regions with a high number of D₂ receptors. An increase in metabolism following neuroleptic treatment is in accordance with the finding that amphetamine decreases glucose metabolism probably by increasing dopaminergic and noradrenergic transmission in the brain⁶². The relationship between clinical improvement and changes in metabolism after neuroleptic treatment cannot be analysed from the available studies, since neither type nor period of treatment were fixed. In a small patient sample ($n=5$) Wik *et al.*⁶¹ found a conspicuous correlation between decrease in depressive symptoms and an increase in metabolism after 5 weeks treatment with sulpiride in a fixed dose (800 mg/day).

Relative rates were found to increase in the right lentiform nucleus and putamen after neuroleptic treatment^{38, 61}. An increase of relative rates in the striatum have also been reported by Szechtman and coworkers⁵² in 5 patients treated with neuroleptic drugs in one year. Higher relative rates in striatum were also found in chronic neuroleptic treated patients (mean 7·4 years). In one study no effect of neuroleptic treatment on subcortical ratios was found³⁵.

In analysing brain metabolism in schizophrenic patients most studies have used chronic patients previously treated with neuroleptics. Obviously it is most important to investigate whether the reduced metabolic rates reported in most studies are related to the disease or previous drug treatment. The effect of the duration of the disease and drug treatment were analysed in one study³⁶. Duration of disease but not duration of neuroleptic treatment was related to the reduced brain metabolism in the schizophrenic patients.

Affective disorders

Two major studies have been performed investigating glucose metabolic rates in affective disorders. Baxter and coworkers⁶³ found that subtypes of depressive disorders had different metabolic rates. Thus, bipolar depressed patients had lower metabolic rates in most parts of the brain (Table 3) than unipolar, bipolar (manic state) patients who did not differ from the controls (Table 3). Both the controls and the patient groups had higher left/right metabolic ratios in frontal cortical areas. This is in accordance with the findings in the controls of other patient studies (see above). Thus a higher left hemisphere activity may be the normal pattern of the human brain. Clinically there are similarities between autistic/negative schizophrenic patients (decreased metabolic rates) and bipolar depressed patients, such as reduced emotional activity, loss of energy, sluggish of thought processes and reduced motor activity. This may indicate that similar neuronal pathways are affected in the 2 diseases for some of the symptoms, but in all probability in a different way, as

Table 3. Regional cerebral glucose metabolism (mol/100 mg × min) in various types of psychiatric disorders

| Regions | n | Controls | | | Patients | | | Setting | | | |
|-------------------------------|-----------|------------------------|------------|-------|----------------------------------|--|------------|---------|---|------------------|------------|
| | | Left | Both sides | Right | n | Left | Both sides | Right | Tracer | FWHM | Ref. |
| Whole brain ⁽¹⁾ | 9 (13) | 23.6±1.9 (25.8±4.3) | | | Depressed unipolar 11 (12) | 24.5±3.0 (24.4±3.0) | | | Rest. cond. ¹⁸ F-DG | 11 mm | 63 (66) |
| Whole brain ⁽¹⁾ | 9 | see above | | | Bipolar manic 5 | 24.7±4.6 | | | | | |
| Whole brain ⁽¹⁾ | 9 | see above | | | Bipolar depressed 6 (11) | 16.7±3.7* (19.2±3.9) | | | | | |
| Frontal cortex ⁽²⁾ | 19 | 29.2±8.3 | | | Depressed 11 11 | 34.5±8.9 34.3±10.3* | | | El. stim. right arm ¹⁸ F-DG | 17.5 mm | 37 |
| Posterior cortex | 19 | 26.5±7.6 | | | Bipolar 16 16 | 26.6±9.0 ⁽³⁾ 24.4±8.7 ⁽³⁾ | | | El. stim. right arm ¹⁸ F-DG | 17.5 mm | 64 |
| Frontal cortex ⁽³⁾ | 24 | 21.3±6.4 | | | Unipolar 4 4 | 32.3±6.2 ⁽³⁾ 25.3±5.9 ⁽³⁾ | | | | | |
| Posterior cortex | 24 | 18.4±6.0 | | | Bipolar 16 16 | 21.3±7.8 25.0±9.3 | | | | | |
| | | see above | | | Unipolar 4 4 | 23.4±3.8 31.0±7.0 | | | | | |
| Caudate ⁽⁴⁾ | 24 | 18.1±5.7 | | | Depressed 5 5 | 19.0±2.7 (s.e.) | | | El. stim. right arm ¹⁸ F-DG | 17.5 mm | 88 |
| Putamen | 24 | 21.4±6.9 | | | Depressed 4 4 | 23.4±3.8 31.0±7.0 | | | | | |
| Caudate ⁽⁴⁾ | 24 | see above | | | | | | | | | |
| Putamen | 24 | | | | | | | | | | |
| Temporal cortex | 18 | 15.1±1.0 (s.e.) | | | | | | | | | |
| | | | | | | | | | | | |
| Whole brain ⁽⁵⁾ | 11 | 2.61±0.42 | | | | | | | Rest. cond. ¹⁵ O | 12.4- 14.7 mm | 89 |
| | | | | | | | | | | | |
| Whole brain ⁽⁶⁾ | 14 | 26.3±4.2 | | | Depressed unipolar 14 | 25.2±3.2 | | | Rest. cond. ¹⁸ F-DG | 11 mm | 24.8±3.2 |
| Orbital gyri | 13 | 28.2±5.1 | | | | 14 | 28.7±3.9 | | | | 29.1±4.2 |
| Caudate nucleus | 14 | 31.7±5.0 | | | | 14 | 29.7±3.4 | | | | 30.7±3.8 |
| | | | | | | | | | | | |
| Obsessive compulsive | 9 | 29.4±3.6* | | | | | | | | | 29.2±3.4* |
| Whole brain ⁽⁶⁾ | 8 | 33.4±5.0* | | | | | | | | | 32.9±4.7* |
| Orbital gyri | | | | | | | | | | | |

see above

Whole brain⁽⁶⁾
Orbital gyri

see above

| | | | | | | | |
|---|-----------|-----------|-----------|--------------------|------------------------------------|------------------|----|
| Whole brain ⁽⁶⁾ | see above | | | | | | |
| Orbital gyri | | | | | | | |
| Caudate nucleus | | | | | | | |
| Whole brain ⁽⁷⁾ | 15 | 2.74±0.41 | | | | | |
| Parahippocampus | 15 | 2.79±0.54 | 2.77±0.59 | | | | |
| Frontal cortex ⁽⁸⁾ | 15 | 45.2±6.4 | 45.0±6.4 | Anorexia nervosa | Rest. cond. ¹⁵ O | 12.4– 14.7 mm | 68 |
| Caudate nucleus | 15 | 43.5±5.1 | 42.9±5.7 | 51.0±4.0** | | | |
| Thalamus | 15 | 39.4±5.1 | 40.2±4.9 | 44.1±3.9 | Rest. cond. ¹⁸ F-DG | 7.8 mm | 71 |
| Brainstem | 15 | 28.6±4.1 | 29.3±4.7 | 33.0±3.6* | | | |
| Prefrontal cortex ⁽⁹⁾ (medial part) | 6 | 39.7±5.9 | | Alcohol dependence | Rest. cond. ¹⁸ F-DG | 7.8 mm | 72 |
| Parietal cortex | 6 | 36.9±5.1 | 38.2±5.1 | 35.2±5.8 | | | |
| Thalamus | 6 | 29.6±6.2 | 29.1±5.1 | 30.1±7.2 | Rest. cond. ¹¹ C-glu | 7.6 mm | 73 |
| Prefrontal cortex ⁽¹⁰⁾ (area 9) | 12 | 24.8±3.1 | | 17.8±4.4** | | | |
| Parietal cortex (area 39+40) | 12 | 25.1±3.4 | | 17.8±5.0** | | | |
| Thalamus | 11 | 23.0±3.2 | | 17.5±3.2* | | | |

Mean ± SD and two tailed Student's t-test. Regions are selected to favour comparisons among groups. Several authors have published their results successively and the cited reference is meant to be the one with the highest number of subjects investigated. Patients were not treated with neuroleptics or antidepressive drugs if not stated otherwise. The different diagnostic groups fulfilled their respective DSM-III diagnosis.

(1) Above the supratentorial level. Controls had higher metabolic rates than bipolar depressed patients in frontal lobes (40%), caudate nucleus (34%) and thalamus (44%) both hemispheres ($p<0.01$, only the % difference was presented). In the bipolar patient group one patient was on medication, and another patient was scanned twice. However, with $n = 4$ (one patient excluded and the 2 scans averaged) the difference was still significant ($p<0.05$). Schwartz *et al.* (1987) presented an extended patient material with the same results as Baxter *et al.* 1985, data within brackets.

(2) Supraventricular slice. The patients were 10 bipolar and one unipolar. All patients were depressed. The patients had higher metabolic rates also in the posterior areas of the mid- and infraventricular slices. * $p<0.05$.

(3) Supra-, mid- and the infraventricular slices. ANOVA showed a diagnostic effect ($p<0.01$) and an anterior-posterior effect ($p<0.001$).

(4) No hemisphere or group effects were statistically significant (neither for thalamus nor for globus pallidus). ** $p<0.01$.

(5) ml/100 g × min (oxygen metabolism) different subtypes of depressed patients. * $p<0.05$. Other regions did not differ between controls and obsessive patients. The depressed patients had significantly lower rates than the obsessive patients in the same regions except for right orbital gyrus.

(6) ml/100 g × min (oxygen metabolism). Patients sensitive to lactate $n = 6$, not sensitive to lactate $n = 8$. * $p<0.05$.

(7) * $p<0.05$, ** $p<0.01$, after weight gain there was no differences between patients (female) and normals (male).

(8) Several regions were investigated, no significant differences between controls and patients were found. No asymmetries.

(9) The patients had a decreased metabolism in 11 regions of 19 examined. No asymmetries were found. * $p<0.05$, ** $p<0.01$.

indicated by the disparate treatments used in the 2 categories of patients. That changes in mood may be coupled to changes in metabolism are supported by the findings by Wik and coworkers⁶¹ in schizophrenics ($n=5$) demonstrating that following sulpiride treatment an increase in metabolism was coupled with a decrease in depressive symptoms. On the other hand regulation of emotional tone and drive must be complex since unipolar depressed patients, with similar symptoms as the bipolar patients, had no changes in their metabolic rates⁶³.

Buchsbaum and coworkers^{37, 64} reported increased metabolic rates both in bipolar and in a small sample of unipolar patients (Table 3). In these studies the patients received a painful electric stimulus of the right forearm in contrast to the studies of Baxter *et al.*^{63, 65} in which the patients were investigated in a resting condition. It is not quite clear from the study of Buchsbaum and coworkers⁶⁴ how many of the patients could be subtyped as depressed, manic or mixed bipolar state. This fact also makes it difficult to compare the studies. No left/right differences were found.

Relative rates seemed to discriminate the unipolar patients from the other categories of depressed patients⁶³. Thus, the relative rate of the caudate nucleus was lower in unipolar depressed patients in comparison to the other groups (Table 4). In a small group of unipolar depressed patients this ratio was normalized following treatment. Again Buchsbaum and coworkers⁶⁴ obtained discrepant results in comparison to Baxter *et al.*⁶³, since the relative rate of the caudate was reduced in bipolars and tended to be so also in the small sample of unipolar patients (Table 4). This group also reported that anterior-posterior ratios were lower in bipolar patients than in unipolar patients and controls.

Evidently, more studies are needed before any conclusions can be drawn regarding metabolic rates in depressive disorders. It is uncertain whether the use of a stimulus during the investigation blurred the picture. A decreased metabolism in bipolar depressed patients seems likely since examination of further cases in the study of Baxter and coworkers⁶³ gave similar results in the extended study⁶⁶.

Obsessive compulsive and panic disorders

Obsessive compulsive disorder and panic disorder differs from the other psychiatric disorders since these 2 disorders have increased metabolic rates (Table 3). In obsessive compulsive disorder the metabolism was increased in the orbital gyri and the caudate nuclei (Table 3)⁶⁵. These areas have been related to the occurrence of obsessive symptoms and severe anxiety and are probably affected following capsulotomy⁶⁷. In panic disorder the oxygen metabolism was increased in the whole brain, but only in the patients who were sensitive to lactate (Table 3)⁶⁸. The increase tended to be more pronounced for the right parahippocampus, but since the whole brain had an increased metabolism, a direct coupling between the function of parahippocampus and anxiety in lactate sensitive patients could be questioned. In

both obsessive compulsive and panic disorders, no coupling between anxiety of the patients during the investigation and metabolism was found. Thus the increases in the metabolism cannot only reflect an increase in arousal or attention of the patients. In fact, anxiety in normals seemed to be related to a reduced metabolism⁶⁹.

In obsessive compulsive disorder relative rates differed from controls only in the orbital gyri (Table 4). This ratio was not influenced following treatment, but the relative rate of the caudate nuclei was significantly increased in the patients who responded favourably to the treatment^{65, 70}. A similar result was found in a small sample of successfully drug treated unipolar depressed patients ($n=4$)⁶³.

In patients with panic disorders sensitive to lactate, the relative oxygen metabolism was higher in the right parahippocampus (Table 4)⁶⁸. It is not possible to estimate whether this difference with respect to controls was exclusive for this region, since left/right ratios were not presented for the other regions.

Anorexia nervosa

In a small sample of female anorectic patients an increased metabolism was found bilaterally in the caudate nucleus (Table 3)⁷¹. Following weight gain and improvement there were no differences in metabolism between patients and controls. It is tempting to speculate that the changes in brain metabolism were related to the anorectic behaviour, and were not secondary to the weight loss or the neuroendocrinological disturbances of the patients.

Alcoholism

The glucose consumption in alcoholics has been investigated in 2 studies (Tables 3, 4). Samson *et al.*⁷² did not find any changes in metabolism with respect to controls. However, a relative decrease in the metabolism was observed in a mediofrontal cortical area of the alcoholics. Wik *et al.*⁷³ observed a decrease in the metabolic rates in 11 of the 19 brain regions studied. The cortical areas had the most pronounced changes (Table 3). Relative rates indicated that the parietal area was most influenced in the alcoholic subjects (Table 4). The discrepancy in results between the 2 studies was probably due to differences in the patients and to the way in which regions of interest were delineated. Wik *et al.*⁷³ studied patients who had more serious sequelae of their alcohol dependence than the other patient group. Regions of interest were delineated from CT images and then transferred to the PET images by Wik *et al.*⁷³, whereas Samson *et al.*⁷² used set of circular regions directly on the PET images, which probably decreased the power of the analysis. It seems reasonable to propose that chronic alcoholics with some kind of sequelae of their abuse suffer from a brain dysfunction.

Table 4. Regional cerebral relative metabolic rates in various types of psychiatric disorders

| Regions | Controls | | | | Patients | | | | Setting | | |
|---|----------|-----------|------------|-----------|--|-----------|---------------------|----------------------|---|---------|------|
| | n | Left | Both sides | Right | n | Left | Both sides | Right | Tracer | FWHM | Ref. |
| Caudate ⁽¹⁾ | 9 | 1.32±0.07 | | | Depressed unipolar 11 1.18±0.09** (12 1.16±0.07) | | | | Rest. cond. ¹⁸ F-DG | 11 mm | 62 |
| Caudate ⁽¹⁾ | 9 | see above | | | Bipolar manic 5 1.24±0.04 | | | | | | (66) |
| Caudate ⁽¹⁾ | 9 | see above | | | Bipolar depressed 5 1.30±0.13 (9 1.27±0.08) | | | | | | |
| Frontal cortex ⁽²⁾ | 19 | | | 1.15±0.08 | Depressed 11 | | 1.09±0.087 | | El. stim. right arm ¹⁸ F-DG | 17.5 mm | 37 |
| Frontal/posterior cortex ⁽³⁾ | 24 | 1.11 | | 1.07 | Bipolar 16 | 1.04 | 1.02 | 1.01* | El. stim. right arm ¹⁸ F-DG | 17.5 mm | 64 |
| Frontal/posterior cortex ⁽³⁾ | 24 | | | see above | Unipolar 4 | | 1.17 | *** | | | |
| Caudate | 24 | | | | Bipolar 16 | | | 0.94±0.15 | | | |
| Putamen | 24 | | | | 16 | | | 1.09±0.15 | | | |
| Caudate | 24 | | | see above | Unipolar 4 | | 0.92±0.16 | | | | |
| Putamen | 24 | | | see above | 4 | | 1.19±0.16 | | | | |
| Prefrontal cortex ⁽⁴⁾ | 6 | 0.92±0.06 | | | Depressed 6 | 0.92±0.02 | | 0.91±0.08 | Rest. cond. ¹⁸ F-DG | 12 mm | 55 |
| Caudate | 6 | 0.99±0.16 | | | 6 | 1.01±0.09 | | 1.00±0.07 | | | |
| Temporal cortex ⁽⁵⁾ | 18 | 0.78±0.03 | | | 0.81±0.03 (s.e.) | 5 | 0.68±0.04 (s.e.) | 0.69±0.02* (s.e.) | El. stim. right arm ¹⁸ F-DG | 17.5 mm | 88 |

| | | | | | | | | | |
|---|----|-----------|------------------------|-----------|-----------|-------------|-----------------------------------|--------------------------------|----|
| Orbital gyri ⁽⁶⁾ | 13 | 1.09±0.06 | 1.11±0.08 | 14 | 1.14±0.05 | 1.17±0.05 | Rest. cond. ¹⁸ F-DG | 11 mm | 65 |
| Orbital gyri ⁽⁶⁾ Caudate ⁽⁷⁾ | 13 | 1.21±0.07 | see above | 1.25±0.09 | 14 | 1.15±0.06* | 1.14±0.07 | | |
| Parahippocampus ⁽⁸⁾ (Left/right side) | 15 | | 1.01±0.07 see above | 6 | 1.23±0.06 | 1.29±0.06 | | | |
| Prefrontal cortex ⁽⁹⁾ (medial part) | 6 | | 1.02±0.06 | 6 | 0.98±0.06 | 1.00±0.05 | 0.93±0.06* | Rest. cond. ¹⁵ O | 68 |
| Parietal cortex | 6 | 0.95±0.06 | | 9 | 1.14±0.05 | 1.08±0.05 | 0.98±0.04 | ¹⁸ F-DG | 72 |
| Prefrontal cortex ⁽¹⁰⁾ (area 9) | 12 | | 1.15±0.05 | 9 | 1.15±0.05 | 1.07±0.05** | 1.07±0.05** | ¹¹ C-glu | 73 |
| Parietal cortex (area 39±40) | 12 | | 1.04±0.11 | 9 | | 1.10±0.09 | | | |
| Thalamus | 11 | | | | | | | | |

Mean ± SD for explanation of presented data see Table 3.

(1) Caudate versus the ipsilateral hemisphere. Right side ratios were not presented (said to be similar to left side ratios). Schwartz *et al.* (66) presented an extended patient material, data within brackets. **p<0.01.

(2) Supraventricular slice. The patients were 10 bipolar and one unipolar. Frontal cortex versus whole slice. No test data presented.

(3) Supraventricular slice, unipolar patients were compared with bipolar patients. **p<0.001. Caudate and putamen versus the 2 slices from which the regions appeared. No hemisphere differences were found. *p<0.05.

(4) The region versus all regions. Several regions were compared. No significant differences were found. Five patients had a unipolar depression. Three of the patients were scanned with and without medication.

(5) Within the temporal lobe slice maximal glucose values versus whole temporal slice. *p<0.05.

(6) Orbital gyri versus ipsilateral hemisphere. The ratios didn't change during treatment either in patients who were successfully or unsuccessfully treated. Test data for depressed patients were not presented. *p<0.05.

(7) Caudate versus ipsilateral hemisphere. Five patients were drug treated. In 8 patients who were successfully drug treated the ratios were increased, right: 1.26±0.06 to 1.34±0.07, left: 1.22±0.04 to 1.29±0.08 (p<0.05).

(8) The ratio of oxygen metabolism in left parahippocampus versus right parahippocampus. Patients sensitive to lactate n = 6 and not sensitive to lactate n = 8. *p<0.05.

(9) The cortical region versus all cortical regions of the same slice. *p<0.05.

(10) The region versus whole brain metabolism. **p<0.01.

Neuroreceptors in Psychiatric Patients

The use of PET for *in vivo* imaging and quantitation of central neuroreceptors will be very fruitful in the study of psychiatric disorders. It will be feasible to test hypotheses linking disturbances in different neuronal systems to specific categories of psychiatric disorders and to study the mechanisms of action of psychotropic drugs. The application of PET in this field has so far been limited mainly by the need to develop appropriate PET models for receptor quantitation and suitable ligands. The most extensively studied receptor system in patients is the dopaminergic one for which models have been developed²²⁻²⁴. A model for quantitation of benzodiazepine receptors using the saturation technique has also been developed, but has not yet been applied to the study of psychiatric patients²⁵.

Schizophrenia

The dopamine hypothesis in schizophrenia is based on 3 major findings:

- (1) Chronic amphetamine abuse may result in a paranoid schizophrenia-like condition.
- (2) Neuroleptic treatment reduces the intensity of psychotic symptoms.
- (3) An increase of D₂-dopamine receptor numbers have been found in postmortem brains from schizophrenic patients.

Together these findings have been suggested to indicate that schizophrenic patients suffer from increased dopaminergic transmission. The finding of an increase in D₂-dopamine receptors in brain tissues from schizophrenic patients is the most convincing argument for this hypothesis⁷⁴. However, postmortem studies include old chronic patients in whom various types of neuroleptics known to increase D₂-dopamine receptor numbers⁷⁵ may have been administered during decades. The possibility of using PET to investigate D₂-dopamine receptors in living psychotropic drug naive schizophrenic patients is therefore of great interest. Two studies have been performed for the quantitation of D₂-receptors in schizophrenic patients, one using a kinetic compartment analysis⁷⁶ and one using the saturation technique⁷⁷. However, the results are contradictory. Wong and coworkers⁷⁶ reported that the patients ($n=10$, $B_{max} = 41.7 \pm 4.6$ pmol/g) had 2.5 times more D₂-receptors in the caudate-putamen than the controls ($n = 11$, $B_{max} 16.6 \pm 2.5$ pmol/g). Farde and coworkers⁷⁷ did not find any difference between the controls ($n = 14$, $B_{max} = 24.6 \pm 6.0$ pmol/ml) and the patients ($n = 15$, $B_{max} = 25.1 \pm 7.0$ pmol/ml). The different models used for the quantitation of D₂-dopamine receptors reflect the differences between the ligands²⁰ (Wong *et al.*⁷⁶ used 3-N (¹¹C)-methylspiperone and Farde *et al.*⁷⁷ used ¹¹C-raclopride). The discrepant results may be due to this fact, but also to differences in patient selection (see 78). In any case, a specific coupling between disturbances in the dopaminergic system and schizophrenia must be questioned,

since Wong and coworkers⁷⁹ also found increases of D₂-receptors in other psychotic disorders.

Other investigators have used the ratio between cerebellum (devoid of any D₂-receptors) and striatum to look for possible changes in D₂-binding sites between controls and patients. Crawley and coworkers⁸⁰ reported in a mixed schizophrenic patient group an increase of 11 per cent of this ratio in patients in comparison with the controls. A gamma camera with 77-Br-spiperone as the tracer was used. Maziere and coworkers⁸¹, using 76-Br-lisuride as the tracer, did not find any difference of this ratio between controls and schizophrenic patients.

Mechanism of actions of antipsychotics

PET allows one to study mechanisms of action of psychotropic drugs. It has been possible to demonstrate that neuroleptic drugs in conventional doses bind to the D₂-dopamine receptors^{24, 82, 83}. Using ¹¹C-raclopride for D₂-receptor quantitation, it was possible to demonstrate that all chemical classes of neuroleptics in conventional doses used in the treatment of schizophrenic patients result in a receptor occupancy in a range of 65 to 85 per cent⁸⁴. A similar level of receptor occupancy was found by Cambon and coworkers⁸² using a semiquantitative method for the determination of the receptor occupancy. As in other receptor systems the receptor occupancy followed a hyperbolic function. Since the conventional doses of neuroleptics result in a receptor occupancy in the more flat part of the curve, a change of the dose will only result in a small change of the receptor occupancy⁸⁴. If D₂-receptor occupancy is mediating the clinical effect, the results indicate that haloperidol in doses of about 6 to 8 mg/day should be therapeutically effective. Such low doses of haloperidol should reduce the risk of extrapyramidal side-effects. It will be of great interest to determine if there is a critical level for receptor occupancy to obtain the anti-psychotic effect, and if such a level is different from the level causing extrapyramidal side-effects.

In vivo saturation analysis by PET in man with ¹¹C-SCH 23390 (a D₁-antagonist) seems to be useful for the quantitative study of D₁-receptor binding²⁸. Studies in a few patients have indicated that the chemical type of the antipsychotic compound determined the level of receptor occupancy⁸⁵. Thus, sulpiride treatment did not result in any D₁-receptor occupancy whereas zuclopentixol and cisflupentixol resulted in a D₁-receptor occupancy of 10 and 35 per cent respectively. Interestingly, the atypical neuroleptic clozapine showed the highest D₁-receptor occupancy, 40 per cent. Clozapine had a higher ratio for D₁- to D₂-receptor occupancy than conventional neuroleptics^{84, 85}.

Depressive states

¹¹C-methylspiperone labels both D₂-receptors and S₂-serotonin-receptors. This ligand could therefore be used to study distribution of S₂-serotonin-receptors in

regions where no D₂-receptors are found. Binding of S₂-serotonin-receptors in neocortical areas was studied in patients in the first year after a stroke. These patients are prone to develop depression. Mayberg and coworkers⁸⁶ found that the severity of depression in left hemisphere stroke patients was negatively correlated to the ratio of binding in left/right temporal cortex. This was not the case for right hemisphere stroke patients. The finding may indicate a coupling between S₂-serotonin-receptor function and some depressive states. However, this must be explored further with radiolabelled ligands selective for S₂-serotonin-receptors.

Acknowledgements

The secretarial assistance is gratefully acknowledged. The study was supplied by grants from the Swedish Medical Research Council (07027, 08318).

References

1. Raichle ME. Cerebral blood flow and metabolism in man: past, present and future. Trends in Neurosci 1980; 3: VI-X.
2. Långström B, Bergson G, Dannals RF, et al. Amino Acids, Peptides and Ligands Labeled with ¹¹C. In: Greitz T, Ingvar DH, Widen L (Eds), The Metabolism of the Human Brain Studied with Positron Emission Tomography. New York: Raven Press, 1985; 93-105.
3. Ter-Pogossian MM, Raichle ME and Sobel BE. Positron-Emission Tomography. Sci Am 1980; 243: 170-181.
4. Walker MD (Ed). Research issues in positron emission tomography. Ann Neurol 1984; 15 (Suppl.).
5. Kennedy C, DesRosiers MH, Jehle JW, Reivich M, Sharpe F and Sokoloff L. Mapping of functional neural pathways of autoradiographic survey of local metabolic rate with ¹⁴C-deoxyglucose. Science 1975; 187: 850-853.
6. Yarowsky PJ and Ingvar DH. Neuronal activity and energy metabolism. Fed Proc 1981; 40: 2353-3262.
7. Sokoloff L. Basic Principles in Imaging of Regional Cerebral Metabolic Rates. In: Sokoloff L (Ed), Brain Imaging and Brain Function. New York: Raven Press, 1985; 21-49.
8. Phelps ME, Huang SC, Hoffman EJ, Selin C, Scklclof L and Kuhl DE. Tomographic measurement of local cerebral glucose metabolic rate in humans with (F-18)2-fluoro-2-deoxy-D-glucose: Validation of method. Ann Neurol 1979; 6: 371-388.
9. Mazziotta JC and Phelps ME. Human Neuropsychological Imaging Studies of Local Brain Metabolism: Strategies and Results. In: Sokoloff L (Ed), Brain Imaging and Brain Function. New York: Raven Press, 1985; 121-137.
10. Reivich M, Alavi A, Wolf A, et al. Glucose metabolic rate kinetic model parameter determination in humans: The lumped constants and rate constants for (¹⁸F) fluorodeoxyglucose and (¹¹C) deoxyglucose. J Cerebral Blood Flow and Metab 1985; 5: 179-192.
11. Blomqvist G, Bergström M, et al. Model for ¹¹C-Glucose. In: Greitz T, Ingvar DH, Widen L (Eds), The Metabolism of the Human Brain Studied with Positron Emission Tomography. New York: Raven Press, 1985; 185-194.

12. Raichle ME, Mintun MA and Herscovitch P. Positron Emission Tomography with ^{15}O xygen Radiopharmaceuticals. In: Sokoloff L (Ed), *Brain Imaging and Brain Function*. New York: Raven Press, 1985; 51-59.
13. Mintun MA, Raichle ME, Martin WRW and Herscovitch P. Brain oxygen utilization measured with ^{15}O radiotracers and positron emission tomography. *J Nucl Med* 1983; 25: 177-187.
14. Mazziotta JC, Phelps ME, Plummer D and Kuhl DE. Quantitation in positron emission computed tomography: 5. Physical-anatomical effects. *J Computer Assisted Tomography* 1981; 5: 734-743.
15. Fox PT, Raichle ME and Thach WT. Functional mapping of the human cerebellum with positron emission tomography. *Proc Natl Acad Sci* 1985; 82: 7462-7466.
16. Fox PT, Raichle ME, Mintun MA and Dence C. Nonoxidative glucose consumption during focal physiologic neural activity. *Science* 1988; 241: 462-464.
17. Kuhar MJ, De Souza EB and Unnerstall JR. Neurotransmitter receptor mapping by autoradiography and other methods. *Ann Rev Neurosci* 1986; 9: 27-59.
18. Sedvall G, Farde L, Persson A and Wiesel FA. Imaging of Neurotransmitter Receptors in the Living Human Brain. *Arch Gen Psychiatry* 1986; 43: 995-1005.
19. Comar D, Maziere M, Godot M, Berger G and Soussaline F. Visualization of ^{11}C -flunitrazepam displacement in the brain of the live baboon. *Nature* 1979; 280: 329-331.
20. Huang SC, Barrio JR and Phelps ME. Neuroreceptor assay with positron emission tomography: Equilibrium versus dynamic approaches. *J Cerebral Blood Flow Metab* 1986; 6: 515-521.
21. Swart JA and Korf J. *In vivo* dopamine receptor assessment for clinical studies using positron emission tomography. *Biochem Pharmacol* 1987; 36: 2241-2250.
22. Wong DF, Gjedde A and Wagner HN. Quantification of neuroreceptors in the living human brain. I. Irreversible binding of ligands. *J Cerebral Blood Flow Metab* 1986; 6: 137-146.
23. Wong DF, Gjedde A, Wagner HN, et al. Quantification of neuroreceptors in the living human brain. II. Inhibition studies of receptor density and affinity. *J Cerebral Blood Flow Metab* 1986; 6: 147-153.
24. Farde L, Hall H, Ehrin E and Sedvall G. Quantitative analysis of D₂ dopamine receptor binding in the living human brain by PET. *Science* 1986; 231: 258-261.
25. Persson A, Pauli S, Halldin C, et al. Saturation analysis of specific ^{11}C Ro 15-1788 binding to the human neocortex using positron emission tomography. *Human Psychopharmacol* 1989; 4: 21-32.
26. Wong DF, Lever JR, Hartig PR, et al. Localization of serotonin 5-HT₂ receptors in living human brain by positron emission tomography using N1-(^{11}C -Methyl)-2-Br-LSD. *Synapse* 1987; 1: 393-398.
27. Blin J, Pappata S, Kiyosawa M, Crouzel C and Baron JC. (^{18}F)Setoperone: a new high-affinity ligand for positron emission tomography study of the serotonin-2 receptors in baboon brain *in vivo*. *Eur J Pharmacol* 1988; 147: 73-82.
28. Farde L, Halldin C, Stone-Elander S and Sedvall G. PET analysis of human dopamine receptor subtypes using ^{11}C -SCH 23390 and ^{11}C -raclopride. *Psychopharmacol* 1987; 92: 278-284.
29. Frost JJ, Mayberg HS, Fisher RS, et al. Mu-opiate receptors measured by positron emission tomography are increased in temporal lobe epilepsy. *Ann Neurol* 1988; 23: 231-237.
30. Holman BL, Gison RE, Hill TC, Eckelman WC, Albert M and Reba RC. Muscarinic acetylcholine receptors in Alzheimer's disease. *In vivo* imaging with iodine 123-labeled 3-quinuclidinyl-4-iodobenzilate and emission tomography. *JAMA* 1985; 254: 3063-3066.

31. Aquilonius SM, Bergström K, Eckernäs SÅ, *et al.* *In vivo* evaluation of striatal dopamine reuptake sites using ^{11}C -nomifensine and positron emission tomography. *Acta Neurol Scand* 1987; 76: 283–287.
32. Garnett ES, Nahmias C and Firnau G. Central Dopaminergic Pathways in Hemiparkinsonism Examined by Positron Emission Tomography. *Can J Neurol Sci* 1984; 11: 174–179.
33. Farde L, Pauli S, Hall H, *et al.* Stereoselective binding of ^{11}C -raclopride in living human brain—a search for extrastriatal central D₂-dopamine receptors by PET. *Psychopharmacol* 1988; 94: 471–478.
34. Wiesel FA, Blomqvist G, Ehrin E, *et al.* Brain Energy Metabolism in Schizophrenia Studied with ^{11}C -Glucose. In: Greitz T, Ingvar DH, Widen L (Eds), *The Metabolism of the Human Brain Studied with Positron Emission Tomography*. New York: Raven Press, 1985; 485–493.
35. Resnick SM, Gur RE, Alavi A, Gur RC and Reivich M. Positron emission tomography and subcortical glucose metabolism in schizophrenia. *Psychiatry Res* 1988; 24: 1–11.
36. Wiesel FA, Wik G, Sjögren G, Blomqvist G, Greitz T and Stone-Elander S. Regional brain glucose metabolism in drug free schizophrenic patients and clinical correlates. *Acta Psychiatr Scand* 1987; 76: 628–641.
37. Buchsbaum MS, DeLisi LE, Holcomb HH, *et al.* Anteroposterior gradients in cerebral glucose use in schizophrenia and affective disorders. *Arch Gen Psychiatry* 1984; 41: 1159–1165.
38. Buchsbaum MS, Wu JC, DeLisi LE, *et al.* Positron emission tomography studies of basal ganglia and somatosensory cortex neuroleptic drug effects: Differences between normal controls and schizophrenic patients. *Biol Psychiatry* 1987; 22: 479–494.
39. Wiesel FA, Wik G, Sjögren I, Blomqvist G and Greitz T. Altered relationships between metabolic rates of glucose in brain regions of schizophrenic patients. *Acta Psychiatr Scand* 1987; 76: 642–647.
40. Borg J, Edström L, Bjerkenstedt L, Wiesel FA, Farde L and Hagenfeldt L. Muscle biopsy findings, conduction velocity and refractory period of single motor nerve fibres in schizophrenia. *J Neurol Neurosurg Psychiatry* 1987; 50: 1655–1664.
41. Goode DJ, Meltzer HY, Crayton JW and Mazura TA. Physiologic abnormalities of the neuromuscular system in schizophrenia. *Schizophr Bull* 1977; 3: 121–138.
42. Hagenfeldt L, Venizelos N, Bjerkenstedt L and Wiesel FA. Decreased tyrosine transport in fibroblasts from schizophrenic patients. *Life Sci* 1987; 41: 2749–2757.
43. Wolkin A, Jaeger J, Brodie JD, *et al.* Persistence of cerebral metabolic abnormalities in chronic schizophrenia as determined by positron emission tomography. *Am J Psychiatry* 1985; 142: 564–571.
44. Volkow ND, Wolf AP, Van Gelder P, *et al.* Phenomenological correlates of metabolic activity in 18 patients with chronic schizophrenia. *Am J Psychiatry* 1987; 144: 151–158.
45. Gur RE, Resnick SM, Alavi A, *et al.* Regional brain function in schizophrenia. *Arch Gen Psychiatry* 1987; 44: 119–125.
46. Ingvar DH and Franzen G. Abnormalities of cerebral blood flow distribution in patients with chronic schizophrenia. *Acta Psychiatr Scand* 1974; 50: 425–462.
47. Sheppard G, Manchanda R, Gruzelier J and Hirsch SR. ^{15}O positron emission tomographic scanning in predominantly never-treated acute schizophrenic patients. *Lancet* 1983; ii: 1448–1452.
48. Buchsbaum MS, Ingvar DH, Kessler R, *et al.* Cerebral glucography with positron tomography. *Arch Gen Psychiatry* 1982; 39: 251–259.

49. Farkas T, Wolf AP, Jaeger J, Brodie JD, Christman DR and Fowler JS. Regional brain glucose metabolism in chronic schizophrenia. *Arch Gen Psychiatry* 1984; 41: 293-300.
50. DeLisi LE, Buchsbaum MS, Holcomb HH, et al. Clinical correlates of decreased anteroposterior metabolic gradients in positron emission tomography (PET) of schizophrenic patients. *Am J Psychiatry* 1985; 142: 78-81.
51. Wolkin A, Angrist B, Wolf A, et al. Low frontal glucose utilization in chronic schizophrenia: A replication study. *Am J Psychiatry* 1988; 145: 251-253.
52. Szechtman H, Nahmias G, Garnett S, et al. Effect of neuroleptics on altered cerebral glucose metabolism in schizophrenia. *Arch Gen Psychiatry* 1988; 45: 523-532.
53. Early TS, Reiman EM, Raichle ME and Spitznagel EL. Left globus pallidus abnormality in never-medicated patients with schizophrenia. *Proc Natl Acad Sci* 1987; 84: 561-563.
54. Volkow ND, Brodie JD, Wolf AP, et al. Brain organization in schizophrenia. *J Cerebral Blood Flow Metab* 1986; 6: 441-446.
55. Kling AS, Metter EJ, Riege WH and Kuhl DE. Comparison of PET measurement of local brain glucose metabolism and CAT measurement of brain atrophy in chronic schizophrenia and depression. *Am J Psychiatry* 1986; 143: 175-180.
56. Carlsson A. Antipsychotic drugs, neurotransmitters, and schizophrenia. *Am J Psychiatry* 1978; 135: 164-173.
57. Peroutka SJ and Snyder SH. Relationship of neuroleptic drug effects at brain dopamine, serotonin, adrenergic and histamine receptors to clinical potency. *Am J Psychiatry* 1980; 137: 1518-1522.
58. DeLisi LE, Holcomb HH, Cohen RM, et al. Positron emission tomography in schizophrenic patients with and without neuroleptic medication. *J Cerebral Blood Flow Metab* 1985; 5: 201-206.
59. Gur RE, Resnick SM, Gur RC, et al. Regional brain function in schizophrenia. *Arch Gen Psychiatry* 1987; 44: 126-129.
60. Volkow ND, Brodie JD, Wolf AF, Angrist B, Russel J and Cancro R. Brain metabolism in patients with schizophrenia before and after acute neuroleptic administration. *J Neurol Neurosurg Psychiatry* 1986; 49: 1199-1202.
61. Wik G, Wiesel FA, Sjögren I, Blomqvist G, Greitz T and Stone-Elander S. Effects of sulpiride and chlorpromazine on regional cerebral glucose metabolism in schizophrenic patients as determined by positron emission tomography. *Psychopharmacol* 1989; 97: 309-318.
62. Wolkin A, Angrist B, Wolf A, et al. Effects of amphetamine on local cerebral metabolism in normal and schizophrenic subjects as determined by positron emission tomography. *Psychopharmacol* 1987; 92: 241-246.
63. Baxter LR, Phelps ME, Mazziotta JC, et al. Cerebral metabolic rates for glucose in mood disorders. *Arch Gen Psychiatry* 1985; 42: 441-447.
64. Buchsbaum MS, Wu J, DeLisi LE, et al. Frontal cortex and basal ganglia metabolic rates assessed by positron emission tomography with (¹⁸F)2-deoxyglucose in affective illness. *J Affect Disord* 1986; 10: 137-152.
65. Baxter LR, Phelps ME, Mazziotta JC, et al. Local cerebral glucose metabolic rates in obsessive-compulsive disorder. *Arch Gen Psychiatry* 1987; 44: 211-218.
66. Schwartz JM, Baxter LR, Mazziotta JC, Gerner RH and Phelps ME. The differential diagnosis of depression. Relevance of positron emission tomography studies of cerebral glucose metabolism to the bipolar-unipolar dichotomy. *JAMA* 1987; 258: 1368-1374.

67. Mindus P, Ericson K, Greitz T, Meyerson BA, Nyman H and Sjögren I. Regional cerebral glucose metabolism in anxiety disorders studied with positron emission tomography before and after psychosurgical intervention. *Acta Radiologica* 1986; Suppl. 369: 444–448.
68. Reiman EM, Raichle ME, Robins E, et al. The application of positron emission tomography to the study of panic disorder. *Am J Psychiatry* 1986; 143: 469–477.
69. Gur RC, Gur RE, Resnick SM, Skolnick BE, Alavi A and Reivich M. The effect of anxiety on cortical cerebral blood flow and metabolism. *J Cerebral Blood Flow Metab* 1987; 7: 173–177.
70. Baxter LR, Thompson JM, Schwartz JM, et al. Trazodone treatment response in obsessive-compulsive disorder—correlated with shifts in glucose metabolism in the caudate nuclei. *Psychopathol* 1987; 20: Suppl. 1; 114–122.
71. Herholz K, Krieg JC, Emrich HM, et al. Regional cerebral glucose metabolism in anorexia nervosa measured by positron emission tomography. *Biol Psychiatry* 1987; 22: 43–51.
72. Samson Y, Baron JC, Feline A, Bories J and Crouzel C. Local cerebral glucose utilisation in chronic alcoholics: a positron tomographic study. *J Neurol Neurosurg Psychiatry* 1986; 49: 1165–1170.
73. Wik G, Borg S, Sjörgen I, et al. PET determination of regional cerebral glucose metabolism in alcohol-dependent men and healthy controls using ^{11}C -glucose. *Acta Psychiatr Scand* 1988; 78: 234–241.
74. Seeman P, Ulpian C, Bergeron C, et al. Bimodal distribution of dopamine receptor densities in brains of schizophrenics. *Science* 1984; 225: 728–731.
75. Mackay AVP, Iversen LL, Rossor M, et al. Increased brain dopamine and dopamine receptors in schizophrenia. *Arch Gen Psychiatry* 1982; 39: 991–997.
76. Wong DF, Wagner HN, Tune LE, et al. Positron emission tomography reveals elevated D₂ dopamine receptors in drug-naïve schizophrenics. *Science* 1986; 234: 1558–1563.
77. Farde L, Wiesel FA, Hall H, Halldin C, Stone-Elander S and Sedvall G. No D₂ receptor increase in PET study of schizophrenia. *Arch Gen Psychiatry* 1987; 44: 671–672.
78. Farde L, Sedvall G, Wiesel FA, Halldin C and Stone-Elander S. Brain dopamine receptors in schizophrenia: PET problems. *Arch Gen Psychiatry* 1988; 45: 598–600.
79. Wong DF. Strategies for *in vivo* quantification of human neuroreceptors by PET. *Psychopharmacol* 1988; 96 (Suppl.): 18.
80. Crawley JCW, Crow TJ, Johnstone EC, et al. Uptake of ^{77}Br -spiperone in the striata of schizophrenic patients and controls. *Nucl Med Commun* 1986; 7: 599–607.
81. Maziere B, Loc'h C, Hantraye Ph, et al. PET imaging of D₂ receptors in the living baboon or human brain in normal and pathological conditions using ^{76}Br -bromolisuride. *Psychopharmacol* 1988; 96 (Suppl.): 19.
82. Cambon H, Baron JC, Boulenger JP, Loc'h C, Zarifian E and Maziere B. *In vivo* assay for neuroleptic receptor binding in the striatum. Positron tomography in humans. *Br J Psychiatry* 1987; 151: 824–830.
83. Smith M, Wolf AP, Brodie JD, et al. Serial (^{18}F)N-methylspiroperidol PET studies to measure changes in antipsychotic drug D₂ receptor occupancy in schizophrenic patients. *Biol Psychiatry* 1988; 23: 653–663.
84. Farde L, Wiesel FA, Halldin C and Sedvall G. Central D₂-dopamine receptor occupancy in schizophrenic patients treated with antipsychotic drugs. *Arch Gen Psychiatry* 1988; 45: 71–76.
85. Farde L, Wiesel FA, Nordström AL and Sedvall G. PET examination of human D₁- and D₂-dopamine receptor characteristics. *Psychopharmacol* 1988; 96 (Suppl.): 79.
86. Mayberg HS, Robinson RG, Wong DF, et al. PET imaging of cortical S₂ serotonin receptors after stroke: Lateralized changes and relationship to depression. *Am J Psychiatry* 1988; 145: 937–943.

87. Jernigan TL, Sargent III T, Pfefferbaum A, Kusubov N and Stahl SM. ^{18}F Fluorodeoxyglucose PET in schizophrenia. *Psychiatry Res* 1985; 16: 317-329.
88. Post RM, DeLisi LE, Holcomb HH, Uhde TW, Cohen R and Buchsbaum MS. Glucose utilization in the temporal cortex of affectively ill patients: Positron emission tomography. *Biol Psychiatry* 1987; 22: 545-553.
89. Raichle ME, Taylor JR, Herscovitch P and Guze SB. Brain Circulation and Metabolism in Depression. In: Greitz T, Ingvar DH, Widen L (Eds), *The Metabolism of the Human Brain Studied with Positron Emission Tomography*. New York: Raven Press, 1985; 453-456.