Eur Arch Psychiatry Clin Neurosci (2005) 255 : 308–312 DOI 10.1007/s00406-005-0563-0

ORIGINAL PAPER

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Hypermetabolic pattern in frontal cortex and other brain regions in unmedicated schizophrenia patients

Results from a FDG-PET study

Received: 13 April 2004 / Accepted: 17 November 2004 / Published online: 18 April 2005

Abstract We report results of a FDG-PET study in 10 patients with schizophrenia (6 unmedicated, 4 never medicated) and 12 healthy age-matched controls. The patients met ICD-10 and DSM-IV criteria for schizophrenia and all reported psychotic, "positive" symptoms when tested. Schizophrenic patients had higher absolute CMRGlu values in almost all quantified regions compared to normal subjects. Using the occipital cortex as the reference region patients showed a hyperfrontal metabolic pattern. Other significant regional differences were found with respect to thalamus, striatum and temporal cortex. The finding of a hyperfrontality in un- and never medicated psychotic schizophrenic patients must be discussed in the light of the psychopathological symptoms of patients when tested, a possible disruption of cortico-striato-thalamic feedback loops and recent findings of a hyperfrontality in experimentally induced psychosis (ketamine- and psilocybin-model of schizophrenia).

Key words hyperfrontality · FDG-PET · schizophrenia

Introduction

The etiology of schizophrenia to date remains unclear. The histological and clinical features of this disorder have been discussed in the light of a neurodevelopmental or a neurodegenerative disorder. Harrison [23] in a comprehensive review concluded that decreased cortical volumes in schizophrenia have been demonstrated with a preferential involvement of the temporal lobe. With respect to subcortical structures only the involvement of the dorsal thalamic nuclei could be established. "Functional neuroimaging data indicate that the pathophysiology of schizophrenia reflects aberrant activity in, and integration of, the components of disturbed circuits involving the prefrontal cortex, hippocampus and certain subcortical structures."

Functional neuroimaging technics including positron emission tomography (PET) are used either to quantify neurotransmitter receptors, visualize the sites of action of drugs or to measure cerebral glucose metabolism (i. e., regional cerebral bloodflow), to study resting brain activity, or map cerebral activation during cognitive or motor tasks. PET imaging of glucose metabolism is of special relevance for studies in schizophrenia. Abnormal glucose metabolism is an indicator of underlying pathology and can be detected by PET imaging using an [^{18}F]deoxyglucose tracer (FDG-PET). A number of hypotheses have been derived from recent functional neuroimaging studies in schizophrenia. While some studies have reported an overactivity of the ventral striatum and medial left temporal structures especially the hippocampus and parahippocampal region to be associated with delusions and/or hallucinations [41], other studies using FDG-PET and SPECT in schizophrenia have repeatedly shown a diminished metabolic rate in the anterior cingulate gyrus [27], the (right) thalamus [6, 10] and a hypofrontality [35, 44]. The latter finding has also been confirmed by cognitive tests indicating frontal or prefrontal dysfunction, such as the Wisconsin Card Sorting Test [3, 4, 18, 36–38, 49] or others [1, 26, 29].

Since patients with predominantly negative symptoms exhibited reduced prefrontal activation compared to patients without negative symptoms, hypofrontality has been related to negative symptomatology in schizophrenia [35].

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Other studies have shown a dysfunction in other brain areas of schizophrenic patients including the basal ganglia [28, 29, 33] and the temporal lobe [19, 31]. More recently dysfunctions in schizophrenia have been linked to a dysregulation in cortico-striato-thalamo-cortical feedback loops that play a major part in regulation of frontal cortical functions [30]. Psychopathology and medication status may play a significant role in brain activity as measured by FDG-PET. A number of recent studies have indicated that only a single dose of an atypical neuroleptic such as risperidone decreases metabolism in ventral striatum, thalamus and frontal cortex [30, 32].

While hypofrontality has repeatedly been linked to negative symptomatology, few PET studies have addressed the function of frontal cortex in un- or never medicated schizophrenics with predominately positive symptoms. Recently Potkin et al. [35] in a PET study were able to demonstrate that negative symptoms were associated with lower glucose metabolic rates compared to patients with positive symptoms. Research in model psychosis has revealed different results: Vollenweider et al. [46–48] using the ketamine and the psilocybin model of psychosis demonstrated a frontal hypermetabolic pattern in FDG-PET.

The current study in a group of non- and never medicated schizophrenics with "positive" symptomatology was performed studying brain resting activity by FDG-PET to examine [1] a possible frontal/prefrontal dysfunction in psychotic schizophrenics [2], reevaluate the possible role of other key structures, especially the striatum and thalamus which had been linked with impaired sensory filter [11], and [3] possible right/left asymmetries of metabolism [21, 22] in schizophrenia.

Methods

FDG-PET

FDG-PET scanning was performed on a Siemens ECAT EXACT HR + PET scanner. The scanner acquires 63 contiguous transaxial planes, simultaneously covering 15.5 cm of the axial field of view. Data acquisition follows a standardized protocol established at the Department of Nuclear Medicine at the University of Munich. Each patient is examined in a fasting state with eyes open, ears plugged, and in a moderately light environment. The head of the patient is fixed in a head holder and adequately positioned in the gantry. Acquisition starts with a 15-minute transmission scan (Ge-68 sources) used for subsequent attenuation correction. After the transmission scan, 120 MBq (F-18)FDG were intravenously administered. A static PET study was obtained from 30 to 60 minutes post-injection (3 frames, 10 minutes/frame, 128 x 128 matrix, 3D acquisition). Images were reconstructed by filtered back projection using a Hann filter with a cut-off frequency of 0.5 Nyquist. Images were corrected for scatter and attenuation. A time activity curve of the FDG concentration in blood plasma was obtained by sampling arterialized venous blood. Images of calculated rCMRGlc were obtained from the reconstructed PET images using the time-activity curve of FDG concentration in plasma and the plasma glucose level according to the method of Phelps et al. using standard rate constants K1 to k4 and a lumped constant of 0.52.

For further evaluation, data were transferred to a work station with Hermes software (Nuclear Diagnostics) which enables one to compare the patient data after stereotactic realignment to a 3-dimensional reference template created from a normal database consisting of 12 patients. Deviations from the normal database may be assessed on the voxel-level evaluating statistical differences using the standard deviation criterion. This approach allows one to compare the baseline status in different individuals with a normal database as well as to assess the intrasubject variation in repetitive studies on the same individual. Data from the set of 63 ROIs covering the whole brain were pooled and combined to separate ROIs for frontal, parietal, temporal, occipital cortex as well as striatum, thalamus, cerebellum and brain stem.

Patient characteristics

Ten inpatients (6 male, 4 female) who met the ICD-10 and DSM-IV criteria for schizophrenia were included in the study. All were unmedicated, four totally drug naive. Mean age was 38.9 years (SD 12.6), all but one were righthanded. Mean duration of disorder since first onset was 47.8 (SD 49) months, age of onset 34.6 (SD 15.7) years, age at first hospitalization was 37.7 (14.1) years. Mean number of previous hospitalizations was 1.9 (SD 1.4). Mean level of education was 12.5 (SD 5.9) years.

Psychopathology: PANSS general score as rated by an experienced psychiatrist at baseline was 39.4 (9.1), PANSS positive score 23.2 (SD 3.8), PANSS negative score 21.9 (SD 8.6).

The control group consisted of 12 age- and sex-matched healthy individuals well known to the researchers and a similar level of education. They were all free of any medication.

Statistics

All statistics have been calculated using the SPSS software package. In addition to the absolute CMRGlu values, ratios between different regions and the occipital cortex have been calculated to compensate for interindividual variation of total metabolic rates. Mean and standard deviation values have been calculated for both absolute CMRGlu values and the ratios to describe the distribution of the data. Student t-tests were used to compare group differences between the patient group and the control group.

Regional metabolic rates of glucose

Compared to the control group, schizophrenic patients had higher absolute CMRGlu values in almost all quantified regions, but none of the differences were significant. Since the standard deviation of the CMRGlu is high in both groups and in all examined regions indicating a high interindividual variation, more attention should be paid to ratios between brain regions and the occipital cortex as reference, referred to as 'metabolic ratios'. These also play an important role in diagnosing a frontal hypo- or hypermetabolic pattern. Table 1 gives an overview of the calculated ratios as well as their standard deviation and also illustrates differences between the patient and the control group.

The patients' mean metabolic ratios were higher than the ones from the control group in all examined areas. Whereas the parietal-occipital ratio differs only slightly between patients and controls

Table 1 Calculated metabolic ratios and standard deviations

	Patient Group		Control Group	
	mean	SD	mean	SD
Frontal/occipital	1.09	0.09	1.02	0.04
Parietal/occipital	1.05	0.06	1.04	0.04
Temporal/occipital	0.94	0.06	0.90	0.03
Thalamus/occipital	0.95	0.05	0.90	0.06
Striatum/occipital	1.13	0.07	1.07	0.04

(1.05 ± 0.06 vs. 1.04 ± 0.04), there is a significant difference of the frontal-occipital ratio (1.09 ± 0.09 vs. 1.02 ± 0.04, $p < 0.05$), which indicates a frontal hypermetabolic pattern.

Furthermore, statistically significant differences were found for the respective ratios for striatum (1.13 ± 0.07 vs. 1.07 ± 0.04), thalamus (0.95 ± 0.05 vs. 0.90 ± 0.06) and the temporal cortex (0.94 ± 0.06 vs. 0.90 ± 0.03). The differences of metabolic ratios of patient studies compared to the control group are also illustrated in Fig. 1. The mean frontal-occipital ratio in patients is 6.7 % higher than that in the control group. Among all examined metabolic ratios this ratio shows the strongest difference between patients and controls.

Looking at the two hemispheres separately revealed all together more significantly different metabolic ratios between patients and controls in the right hemisphere than on the left side. To compare the examined cortex areas directly between the two hemispheres, we calculated additional right to left ratios for each region, which did not show any statistically significant different patterns between patients' and control studies (Table 2).

Table 2 Calculated metabolic ratios for the two hemispheres

	group			
	patients		controls	
	Mean	SD	Mean	SD
r/l ratio frontal	0.99	0.03	1.00	0.02
r/l ratio parietal	1.00	0.04	1.01	0.03
r/l ratio temporal	1.01	0.07	1.00	0.03
r/l ratio occipital	0.98	0.05	0.99	0.03
r/l ratio striatum	0.99	0.07	0.97	0.04
r/l ratio thalamus	1.02	0.06	0.99	0.04

Discussion

Results of the FDG-PET study in a group of un- or never medicated schizophrenics with vivid "positive" symptomatology suggest that patients exhibit a hypermetabolism in various brain regions, especially the frontal cortex ("hyperfrontality") and to a lesser extent also in other regions of interest especially the thalamus, striatum and temporal lobe. No right/left asymmetries could be demonstrated. A number of limitations have to be addressed: Findings of this study are clearly limited by the comparatively small number of patients included. In addition, the implementation of cognitive tasks which usually lead to an activation of the frontal lobe like the Wisconsin Card Sorting Test or others may have led to more significant results. Likewise, an exact measurement of anatomical structures using magnetic resonance imaging (MRI) and a PET-MRI overlay with modeling of PET findings with anatomical structures such as the thalamus as performed by Buchsbaum et al. [7] may have resulted in additional information. There also exist various software programs to analyze functional neuroimaging data which may have shown different results. Still the applied procedure using the occipital cortex as a reference region is a frequently used and well-established method. Finally, the mean age of patients studied was comparatively high. Studies in younger patients with a more chronic course may have shown different results.

Still the findings of this study point at frontal lobe dysfunction in schizophrenia and should be discussed with respect to recent findings and publications in this area. While a number of other functional neuroimaging studies in schizophrenia discussed below have led to the concept of hypofrontality as a trait or state marker in schizophrenic patients, especially with negative symptomatology [1, 2, 17, 34] recent findings by Vollenweider et al. [46–48] point at an increased activation of the frontal cortex ("hyperfrontality") during experimentally induced psychosis using the ketamine and psylocybin-model of psychosis. In addition, a frontal hypermetabolic pattern has been described in some other studies in drug-naive patients with acute symptoms [13, 15, 20, 34, 40, 43, 45]. Andreasen [2] in a landmark study on this subject reported that a decreased frontal activation could be demonstrated in patients with high scores for negative symptoms only. Sabri et al. [39] found both hyperperfusion and hypoperfusion patterns in never-treated patients using SPECT. Positive symptoms correlated positively with rCBF in various regions including the frontal cortex. The finding of a 'hyperfrontality' may be interpreted as a result of a disruption of the cortico-striato-thalamic feedback loops controlling a thalamic filter function [12] that may lead to a sensory overload of the frontal cortex and its limbic relay stations.

Current data indicate that a reduced activity in the frontal cortex and thalamus can at least not consistently be shown in unmedicated patients. In addiction, hyperfrontality and dysfunction of the right thalamus have

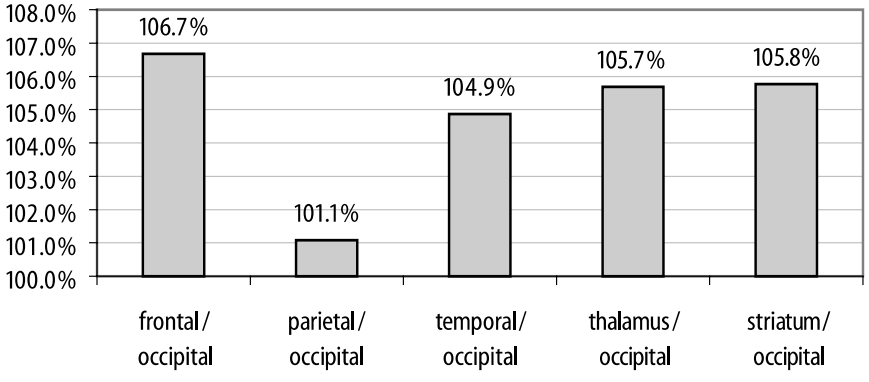

Fig. 1 Percentage of patients CMRGlu ratios compared to control group

also been described in alcohol hallucinosis, a rare disorder which closely resembles paranoid schizophrenia [42], further questioning the specificity of this finding for schizophrenia.

Findings in neuroimaging studies in schizophrenia are subject to a number of variables including patients' psychopathology and medication status [14] and different imaging techniques applied, among others. With respect to FDG-PET studies the significant effects of typical or atypical neuroleptics in schizophrenia have been demonstrated in a number of studies and clearly underscore the importance of medication effects in neuroimaging studies in schizophrenia. A single dose of the atypical neuroleptic risperidone was already found to significantly decrease metabolism in ventral striatum, thalamus and frontal cortex [32]. A reduction of frontal metabolism by neuroleptics has repeatedly been reported [3, 8, 16, 50].

In conclusion despite of the methodological limitations discussed above, data from this study suggest a hypermetabolic pattern in various brain regions of drug-naive schizophrenic patients with predominantly positive symptoms, especially the frontal cortex. Future longitudinal studies may further explore possible associations of psychopathology with metabolic status as measured by PET and effects of medication, among others.

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