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Cerebral metabolic activity correlates of subsyndromes in chronic schizophrenia

Johannes Schröder [a], Monte S. Buchsbaum [b,*], Benjamin V. Siegel [b], Franz Josef Geider [c], James Lohr [d], Cheuk Tang [e], Joseph Wu [e], Stephen G. Potkin [e]

[a] *Department of Psychiatry, University of Heidelberg, Heidelberg, Germany* [b] *Department of Psychiatry, Mount Sinai School of Medicine, Box 1505 New York, 10029 NY, USA* [c] *Department of Psychology, Methodological Branch, University of Heidelberg, Heidelberg, Germany* [d] *Department of Psychiatry, University of California, San Diego, CA, USA* [e] *Department of Psychiatry, University of California, Irvine, CA, USA*

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Abstract

Seventy-nine patients with schizophrenia and 47 healthy controls received positron-emission tomography (PET) with ^{18}F-2-deoxyglucose uptake while executing the Continuous Performance Test (CPT). Patients had been off all psychoactive medication for at least four weeks. Patients' symptoms were assessed with the Brief Psychiatric Rating Scale and factor scale scores were obtained. These scores were used in cluster analysis to identify patients with predominantly delusional, negative, disorganized, and remitted symptoms. To address the interconnective nature of cerebral functioning, regions of interest were defined on the basis of the results of a factor analysis of metabolic rate in selected brain regions. This procedure identified six cortical and eight subcortical region of interest factors. Metabolic rate factor scale scores were compared between the patients' clusters and the healthy controls. The delusional cluster showed a significantly reduced hippocampal activity, while the negative symptoms cluster presented with a prominent hypofrontality and significantly increased left temporal cortex values. Concurrently, both clusters were associated with a decreased activity on the factor 'anterior cingulum and medial frontal gyrus'. The disorganized cluster was characterized by a significant overactivity in the parietal cortex and motor strip and a decreased activity in the corpus callosum. The subsyndromes of chronic schizophrenia are therefore characterized by deviant patterns of cerebral activity rather than deficits in a single location.

Keywords: Positron emission tomography; Subsyndrome; Hypofrontality; Metabolic activity pattern; (Schizophrenia)

1. Introduction

Factor analytic studies of the symptoms of schizophrenia have generally been consistent in identifying three subsyndromes in chronic schizophrenia (Arndt et al., 1991; Aubin et al., 1991; Bilder et al., 1985; Peralta et al., 1992; Liddle, 1987a; Schröder et al., 1992a). The first, a chronic delusional subsyndrome, is characterized by persisting delusions and hallucinations. The second is the chronic negative (or deficit) subsyndrome with a lack of drive and emotional withdrawal. The third is the chronic disorganized subsyndrome with

* Corresponding author. Tel: +1 (212) 241-5294; fax: +1 (212) 423-0819; e-mail: mbuchsba@petlab.mssm.edu.

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prominent formal thought disorders, inappropriate affect and changes of drive. These findings facilitate a differentiation of the positive domain into two subsyndromes (Arndt et al., 1991; Peralta et al., 1992) and thus may be used to further elucidate the heterogeneity of cerebral changes in schizophrenia.

Positron emission tomography (PET) data have identified underlying neuroanatomical information about these subsyndromes. The negative subsyndrome may be caused by frontal lobe dysfunction, in particular of dorsolateral and medial frontal regions: two studies reported an association between negative symptoms and reduced metabolism (Wolkin et al., 1992) or reduced blood flow (Liddle et al., 1992) in the dorsolateral prefrontal cortex, while others found medial frontal lobe impairment to contribute to negative symptoms (Andreasen et al., 1992). Morphological evidence that the medial frontal lobe is involved in the pathogenesis of negative symptoms also comes from a magnetic resonance imaging (MRI) study (Williamson et al., 1991) which reported an increased T2 relaxation time in medial frontal relative to medial temporal areas. In a computed tomography study, Schröder et al. (1992a) found individuals with high scores on a Brief Psychiatric Rating Scale (BPRS; Overall and Gorham, 1962) derived factor for negative symptoms and for delusional symptoms to show a widening of the frontal interhemispheric fissure, consistent with the medial frontal activity decreases described in a recent PET study by Siegel et al. (1993).

The delusional subsyndrome may be related to the temporal lobe. Two studies (DeLisi et al., 1989; Buchsbaum et al., 1990) found BPRS ratings of hallucinations correlated with left temporal activity. These finding were recently confirmed by Liddle et al. (1992) who reported an association between delusional symptoms and an increased left temporal blood flow.

Evidence regarding the disorganized subsyndrome is equivocal: Liddle et al. inferred from a neuropsychological (1987b) and a PET (1992) study that formal thought disorders may refer to prefrontal lobe dysfunction. However, the neuropsychological results were only partly replicated by Brown and White (1991).

Several studies have consistently reported an association between neurological soft signs and formal thought disorders which are the core symptoms of the disorganized subsyndrome (Liddle, 1987a; Schröder et al., 1992a; Torrey, 1980). Therefore, one might expect areas important for the generation of motor activity to be involved in the disorganized subsyndrome.

The specificity of these cerebral changes for the respective subsyndromes was recently addressed by two studies (Liddle et al., 1992; Schröder et al., 1992a). While establishing distinct relations between subsyndromes and cerebral sites, both studies share one major drawback; patients were on neuroleptics when investigated. Therefore one may ask whether these findings reflect symptoms nonresponsive to medication rather than preexisting psychopathological entities.

At this point, one methodological issue has to be stressed: how can the relation between psychopathological subsyndromes and PET measures be investigated? Two strategies may be adopted: first, correlation coefficients may be calculated between subsyndrome scores and PET variables. This design is limited by the fact that correlation coefficients can only be evaluated for subjects who do show psychopathological symptoms, but not for healthy controls in whom psychopathological variables are not defined. A second difficulty with examining correlations is that the number of potential candidate PET variables is large and there is a risk of Type I statistical error. The number of PET variables may be reduced by factor analysis if the subject population is sufficiently large, as in the current sample which is to our knowledge the largest sample of uniformly scanned, unmedicated patients.

Alternatively, the subsyndromes may be used to identify subgroups of patients, each representing one subsyndrome. In a second step, these subgroups may be directly compared with each other and a control group on the PET variables.

The aims of our study were: first, to examine the subsyndromes of chronic schizophrenia with respect to their possible cerebral sites using ^{18}F-2-deoxyglucose PET in unmedicated patients; and second, to investigate the question of whether the

subsyndromes refer to patterns of cerebral activity or localized, structure specific changes.

2. Materials and methods

2.1. Subjects

Seventy-nine patients with a DSM III (APA, 1980) diagnosis of schizophrenia (mean age 30.4 years, SD = 8.6, mean age of onset 23.9 years, SD = 7.3, mean duration of illness 6.7 years, SD = 5.6, 72 men and 7 women) participated in the study. Patients were recruited from the clinical and research programs of the University of California at Irvine (UCI), Los Angeles (UCLA) and San Diego (UCSD) and had been off psychoactive medication for at least 30 days. All, except for 7 patients, were right-handed. Particular care was taken to exclude patients with any history of neurological disorders or substance abuse. In the week before the PET examination psychopathological symptoms were assessed using the Brief Psychiatric Rating Scale (BPRS, Overall and Gorham, 1962; Lukoff et al., 1986). Data from a slightly larger group of these patients had previously been used in cortical surface factor analysis (Schröder et al., 1994); this study reports on data from 79 (of the original 83) who had BPRS assessment.

Forty-seven right-handed volunteers served as a control group (mean age 30.2 years, SD = 9.7). Subjects and patients were screened for health, by history, physical examination and laboratory testing.

2.2. Positron emission tomography

Regional brain activities were imaged as glucose metabolic rate using sterile, pyrogen-free ^{18}F-2-deoxyglucose, prepared as described elsewhere (Buchsbaum et al., 1989).

To control the psychological state during the ^{18}F-2-deoxyglucose uptake all subjects executed the degraded-stimulus Continuous Performance Test (CPT; Nuechterlein et al., 1983). Single digits (0–9) were presented for 40 ms at a rate of one every two seconds on a 24 cm × 24 cm screen. Subjects were asked to press a button with their right hand every time a zero occurred. They were instructed to respond to the target with the same attentiveness as to neglect the non-targets. Targets were presented randomly, with a probability of occurrence at $p = 0.25$.

To minimize head movement, a thermosetting plastic head holder was fitted to each subject. For the ^{18}F-2-deoxyglucose uptake, subjects were seated in a darkened room. An intravenous line of 0.9% saline drip was inserted into the subject's left arm for blood sampling; a second line was placed into the right arm for the injection of the labelled glucose. The left arm was wrapped in a hot pack for arterialization of venous blood. All subjects were instructed on the CPT task before injection and were given trials to ensure their comprehension of the task. Two to three minutes before the ^{18}F-2-deoxyglucose injection (4–5 mCi), room lights were extinguished and the CPT was started; the CPT was continued for 32–37 min after the injection. All subjects remained quiet and cooperative. After 30 to 35 min of ^{18}F-2-deoxyglucose uptake, the subjects were transferred to the adjacent scanning room. Between 45 and 100 min after ^{18}F-2-deoxyglucose injection nine planes (CTI NeuroECAT) at 10 increments and parallel to the canthomeatal line (CM) were taken.

Scans were performed with both shadow and septa shields in a configuration with measured in-plane resolution of 7.6 mm and 10.9 mm resolution in the z-dimension (axial). A calculated attenuation correction and a smoothing filter were used. The scanner was calibrated each scan day, with a cylindrical phantom, and compared with well-counter data. Scan data were converted to glucose metabolic rate (Buchsbaum et al., 1989).

2.3. PET variables

Cerebral activity was measured in twenty-seven box shaped regions of interest, placed at representative sites in these regions (Fig. 1).

In addition, cortical activity on each hemisphere was measured in sixteen cortical regions of interest (Fig. 2) using a modification of our cortical peel technique (Buchsbaum et al., 1989).

Regional glucose use was expressed as relative

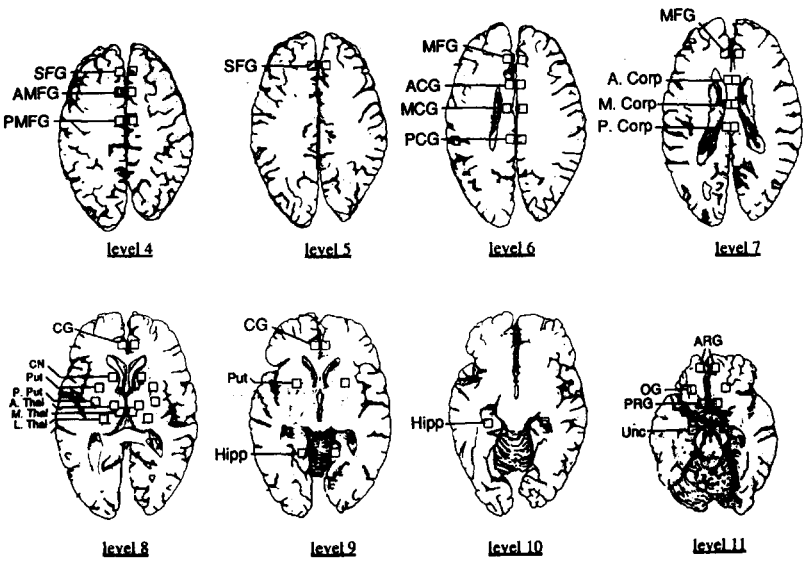

Fig. 1. Key figure for the 27 subcortical regions of interest. SFG = superior frontal gyrus, AMFG = anterior medial frontal gyrus, PMFG = posterior medial frontal gyrus, ACG = anterior cingulum gyrus, MCG = medial cingulum gyrus, PCG = posterior cingulum gyrus, A. Corp. = anterior corpus callosum, M. Corp. = middle corpus callosum, P. Corp. = posterior corpus callosum, CG = cingulum gyrus, CN = caudate nucleus, Put = putamen, P. Put = posterior putamen, A. Thal. = anterior thalamus, M. Thal. = medial thalamus, L. Thal. = lateral thalamus, Hipp. = hippocampus, ARG = anterior rectal gyrus, OG = orbital gyrus, PRG = posterior rectal gyrus, Unc = uncus.

glucose metabolic rate (GMR), which is defined as the ratio of regional GMR to whole brain GMR.

2.4. Data analysis

All statistical computations were performed using the SAS (SAS Institute, 1990) statistical package.

Subgrouping the patients' sample. The subsyndromes of chronic schizophrenia were assessed using the four BPRS factors scales derived from a previous study (BPRS factor 'delusional ideation': somatic concern, anxiety, hostility, suspiciousness, hallucinatory behavior and unusual thought content; BPRS factor 'negative symptoms': emotional withdrawal, motor retardation and blunted affect; BPRS factor 'disorganization': conceptual disorganization, tension, excitement, mannerism and posturing; BPRS factor 'depressive': guilt feelings, depressive mood and–negatively correlated–grandiosity; Schröder et al., 1992a). Subsyndrome scores were subjected to a cluster analysis (SAS: Proc fastclus) that generated disjunct clusters based on unweightened classification variables. Subsequently, the schizophrenic subgroups and the control group PET data were compared. For each group, means and standard deviations were calculated and analyses of variance were performed (SAS: Proc GLM).

2.4.1. Analysis of PET variables

For the analysis of PET images, it is necessary to summarize the activity measured in different regions of interest. This may be done by averaging those regions of interest constituting anatomical area or system if these are known in advance. This strategy minimizes problems with multiple statistical comparisons and type I error, but does not consider the interconnective nature of cerebral organization as would factor analytic approaches (Volkow and Tancredi, 1991). In the present study, principal component factor analysis with VARIMAX-rotation (SAS: Proc factor) was used to investigate cerebral activity for underlying dimensions. The number of factors retained was determined by analyzing the scree plot and by using the eigenvalue criterion (Bernstein, 1988;

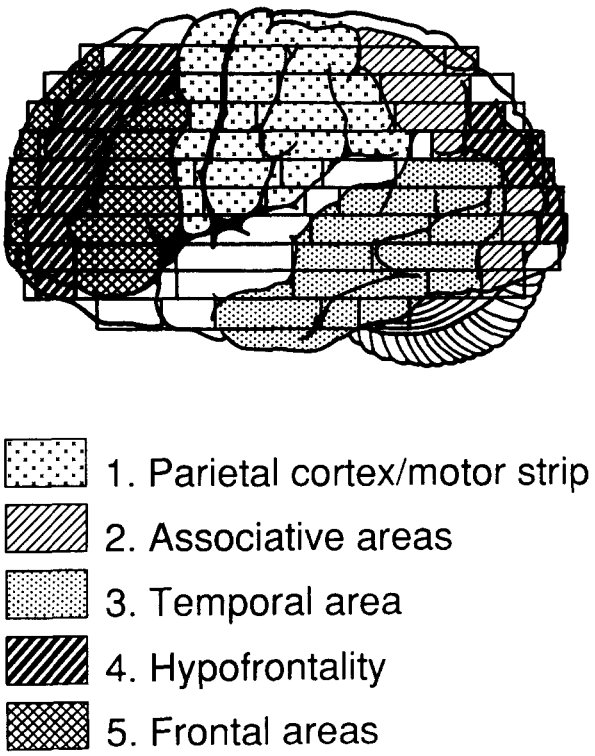

Fig. 2. Key figure for five cortical area factors identified by factor analysis from sixteen cortical regions of interest (four major gyral divisions in the frontal, parietal, temporal and occipital lobes as described in Schröder et al., 1994). Descriptive names for each factor given below. Each texture identifies areas which show high weights on each factor. Coherent regional clustering of factor loading is generally seen, except for the associative area factor and the hypofrontality factor. Note the presence of the hypofrontality factor (factor 4, heavy stripes) with negative frontal and positive occipital loading (see text). The sixteen regions were derived (Siegel et al., 1992) as four from each lobe: frontal (superior, middle, inferior, precentral gyrus), parietal (post-central, supramarginal, superior parietal lobule, angular gyrus), temporal (superior, middle, inferior and posterior regions) and occipital (superior and inferior area 17, area 18 and 19).

Geider et al., 1982). For optimizing the critical ratio between sample size and number of variables, we decided to reduce the latter by calculating two factor analyses, one each for the subcortical and the cortical data, respectively. The original comprehensive set of 63 brain areas (Siegel et al., 1992) was reduced to 27 (Fig. 1) by selecting areas in the medial frontal, striatal, thalamic and limbic systems thought relevant to circuit deficits in schizophrenia (see Swerdlow and Koob, 1987; Carlsson and Carlsson, 1990). Furthermore, means of corresponding regions in the right and left hemispheres were computed; this yielded 27 subcortical and 16 cortical variables resulting in a number of observations/number of variables ratio of >3 and >5,respectively. This was done with the data of the schizophrenic patients, since the regions of interest were placed in morphological sites important for schizophrenia and the variance associated with the three subsyndromes would only be found in the patient group. The identified factors allowed for the calculation of factor scales as recommended by Bernstein (1988) and Geider et al. (1982). Scores for each factor were calculated for each individual patient by averaging the items weighing 0.50 or above.

For analysis of the cortex, we applied the factor structure reported previously on this same sample (Schröder et al., 1994). In this study, six factor scores (Fig. 2) were calculated: parietal cortex and motor strip, associative areas, left temporal cortex, right temporal cortex, hypofrontality (which included midfrontal and occipital areas) and frontal cortex.

In order to address the relationship between severity of illness, duration of illness and the factors, Pearson correlations were calculated (SAS: Proc corr). The duration of illness was corrected for age, because time elapsed since the onset of symptoms should correlate with chronological age. Since the control group included a larger proportion of females than the patients' sample, we compared the factor scale values between female and male controls.

3. Results

3.1. Subgroups

Using a cluster analysis with the BPRS factor (subsyndrome) scales from our previous study (Schröder et al., 1992a) as classification variables, the patient sample was separated into four clusters (Table 1).

Cluster 1 patients were characterized by the highest scores on the delusional ideation factor,

Table 1
Means and standard deviations as descriptive parameters of the subgroups: results of a cluster analysis creating four disjunct subgroups by using the BPRS factor scales as classification variables

Cluster:	BPRS factor scales							
	Delusional		Negative		Dis-organization		Depression	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Delusional	4.19	0.70	3.06	1.11	2.36	0.77	1.20	0.80
Negative symptoms	2.00	0.50	4.12	0.89	2.26	0.73	0.92	0.75
Disorganized	3.30	0.98	2.00	0.84	2.50	0.79	0.65	0.79
Remitted	1.75	0.47	1.76	0.56	1.56	0.48	0.61	0.47

cluster 2 patients presented with the highest scores on the negative symptoms factor; these two clusters were labelled as 'delusional' and 'negative symptoms', respectively. Cluster 3 patients scored highest on the disorganization factor but also showed high scores on the delusional factor. This cluster was therefore labelled 'disorganized'. Cluster 4 patients showed low values on all BPRS factor scores and were labelled cluster 'remitted'. The three chronic clusters encompassed 57 patients (delusional = 14, negative symptoms = 21, disorganized = 22), whereas the cluster remitted comprised 22.

3.2. PET variables

Following the inspection of the scree plot and the eigenvalue criterion, the factor analysis of the twenty-seven subcortical regions of interest revealed eight factors, these accounting for 71% of the common variance (Table 2).

The regions of interest placed in the anterior, medial, and lateral thalamus and the ventral putamen showed high loadings on factor 1. This factor was labelled 'thalamus'. Factor 2 encompassed the putamen and head of the caudate and (negatively correlated) two regions placed in the superior frontal gyrus and was therefore labelled 'fronto-striatal system'. Factor 3 was labelled 'anterior cingulum and medial frontal gyrus', factor 4 'cingulum', as they consisted of the regions of interest localized in the respective brain areas. The PET regions orbital gyrus, anterior and posterior rectal gyrus made up factor 5 which was labelled 'orbitofrontal lobe'. Factor 6 ('anterior and posterior medial frontal gyrus') enclosed the 'anterior' and the 'posterior medial frontal gyrus'; factor 7 ('corpus callosum'), the three regions placed in the anterior, medial and posterior parts of the corpus callosum. Factor 8 ('hippocampus') showed high loadings on the regions placed in the hippocampus and the uncus.

The factors corpus callosum, frontal cortex and hypofrontality were significantly ($p<0.05$) correlated with age ($r=-0.25$, $r=-0.39$ and $r=0.41$; respectively); the factors anterior cingulum and medial frontal gyrus, thalamus and hypofrontality correlated with the duration of illness ($r=0.25$, $r=0.38$ and 0.39, respectively, $p<0.05$). When the duration of illness was corrected for age, the correlations for the thalamus and hypofrontality remained significant ($r=0.37$ and $r=0.25$, $p<0.05$; respectively). No significant correlations between any of the factors and the severity of illness (total BPRS-score) were found.

Mean values of the various clinical characteristics of the schizophrenic subgroups are given in Table 3. No age differences were found between patients and healthy controls; within the patients' sample the negative symptoms cluster presented with the significantly ($p<0.05$) longest duration of illness ($F=2.87$, df = 3; $p<0.05$) at the lowest age of onset ($F=3.64$, df = 3; $p<0.05$).

The four schizophrenic subgroups and the healthy controls differed significantly on six of the fourteen cortical and subcortical activity factors (Fig. 3): parietal cortex and motor strip ($F=3.59$, df = 4; $p<0.01$); left temporal cortex ($F=2.54$, df = 4; $p<0.05$); hypofrontality ($F=4.28$, df = 4; $p<0.005$); anterior cingulum and medial frontal

Table 2
Factor loadings for the subcortial regions of interest (varimax-rotated factor pattern)

	Factor 1	Factor 2	Factor 3	Factor 4	Factor 5	Factor 6	Factor 7	Factor 8
Anterior thalamus	0.85	−0.23	−0.03	0.12	0.07	0.06	0.14	0.19
Medial thalamus	0.81	0.22	0.12	0.21	0.06	0.08	0.05	0.11
Lateral thalamus	0.82	−0.16	−0.11	−0.15	−0.12	−0.02	−0.26	−0.03
Putamen, level 9	0.61	−0.15	−0.26	−0.04	0.14	0.27	−0.01	−0.13
Superior frontal gyrus, level 4	0.24	−0.50	0.27	−0.01	0.24	0.41	0.15	0.07
Superior frontal gyrus, level 5	−0.01	−0.66	0.07	−0.07	0.14	0.38	−0.07	0.07
Putamen, level 8	−0.24	0.70	−0.30	−0.13	0.05	0.21	−0.16	0.35
Posterior putamen	−0.11	0.73	−0.20	−0.08	0.09	0.25	−0.25	0.15
Caudate	−0.03	0.71	0.11	−0.04	−0.14	0.26	0.08	−0.17
Medial frontal gyrus, level 6	0.16	−0.16	0.56	0.17	0.17	0.12	−0.32	0.15
Medial frontal gyrus, level 7	0.12	−0.08	0.79	0.10	−0.01	0.16	0.08	−0.24
Cingulate gyrus, level 8	−0.05	−0.21	0.80	−0.03	0.20	0.07	0.07	0.06
Cingulate gyrus, level 9	−0.23	0.12	0.72	−0.07	0.17	0.08	0.06	0.33
Anterior cingulate gyrus	−0.05	0.15	0.14	0.83	−0.11	0.17	0.04	0.01
Middle cingulate gyrus	0.01	−0.12	0.03	0.85	0.05	−0.06	0.34	0.03
Posterior cingulate gyrus	0.17	−0.14	−0.08	0.84	−0.16	0.04	0.02	−0.00
Anterior rectal gyrus	−0.22	−0.09	0.22	−0.04	0.73	−0.07	0.12	0.07
Orbital gyrus	−0.05	−0.01	−0.01	−0.08	0.85	0.05	−0.05	0.05
Posterior rectal gyrus	0.03	−0.06	0.23	−0.17	0.82	0.01	−0.15	−0.07
Anterior medial frontal gyrus	0.10	0.10	0.11	0.06	0.10	0.82	0.02	−0.07
Posterior medial frontal gyrus	0.12	0.11	0.14	0.09	−0.19	0.72	−0.06	0.09
Anterior corpus callosum	−0.04	0.00	0.19	0.40	−0.12	−0.05	0.65	−0.22
Middle corpus callosum	−0.22	0.09	−0.17	0.03	0.11	0.08	0.69	0.37
Posterior corpus callosum	0.19	−0.23	0.05	0.14	−0.06	−0.03	0.78	0.03
Hippocampus, level 11	0.13	0.05	0.13	−0.07	0.07	−0.22	0.08	0.78
Hippocampus, level 10	−0.02	0.19	0.08	−0.22	−0.45	0.33	0.02	0.44
Uncus	0.08	−0.16	0.00	0.22	−0.06	0.32	−0.00	0.56
Percent of variance	10.5	9.9	9.3	9.6	9.2	7.8	7.4	6.6

Table 3
Means and standard deviations as clinical characteristics of the four subgroups and the results of a Duncan Test at the 5% level

Cluster	Age at examination		Age at onset		Duration of illness	
	Mean	SD	Mean	SD	Mean	SD
delusional(g1)	33.4	11.0	27.5	11.6	5.9	5.8
negative(g2)	30.2	8.7	20.1	4.5	9.5	6.1
disorganized(g3)	29.6	7.3	25.7	6.3	4.5	5.1
remitted(g4)	30.2	5.6	23.0	4.9	7.2	4.6
Duncan Test	no effect		g1, g3 > g2		g2 > g3	

gyrus ($F=2.70$, df=4; $p<0.05$); corpus callosum ($F=2.93$, df=4; $p<0.05$) and hippocampus ($F=2.88$, df=4; $p<0.05$).

Clusters did not differ significantly on the factors thalamus, fronto-striatal system, cingulum and orbito-frontal lobe, anterior and posterior medial frontal gyrus, associative areas, right temporal cortex and frontal cortex.

When all patients were merged into a single group and subsequently contrasted with the healthy controls the differences on the factors parietal cortex and motor strip ($F=4.55$, df=1; $p<0.05$), left temporal cortex ($F=5.42$, df=1; $p<0.05$), hypofrontality ($F=4.71$, df=1; $p<0.05$), corpus callosum ($F=7.85$, df=1; $p<0.005$) and hippocampus ($F=9.80$, df=1; $p<0.005$) were confirmed.

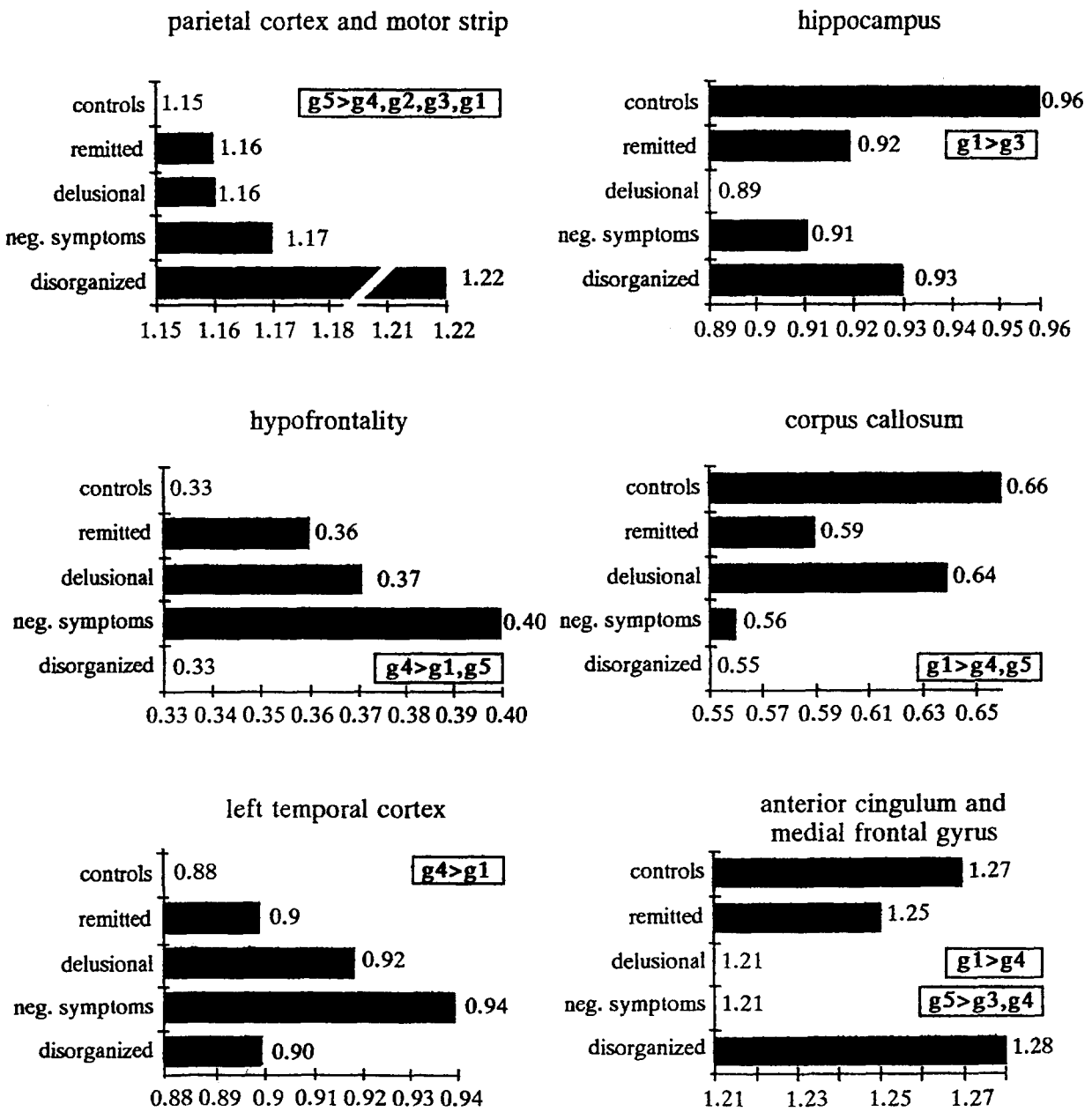

Fig. 3. Profiles of the subgroups on the cortical and subcortical PET variables and the results of a Duncan Test at the 5% level (controls = g1, remitted = g2, delusional = g3, negative symptoms = g4, disorganized = g5). If the remitted subgroup (g2) is omitted, then the following results are obtained: Parietal cortex and motor strip (g5 > g3,g1), hypofrontality (g4 > g5,g1), left temporal cortex (g4 > g1), hippocampus (g1 > g4,g3), corpus callosum (g1 > g4,g5), anterior cingulum and medial frontal gyrus (g1,g5 > g3,g4).

The factor anterior cingulum and medial frontal gyrus, which varied significantly between the clusters, failed to differ significantly between the entire patients' group and the controls ($F = 2.88$, df = 1; $p = 0.09$), whereas the factor cingulum gyrus gained significance ($F = 4.29$, df = 1; $p < 0.05$). Only the factors thalamus and fronto-striatal system varied significantly between male and female con-

trols ($F=10.55$, df = 1; $p<0.005$ and $F=6.67$, df = 1; $p>0.05$, respectively).

4. Discussion

Our study provides three main findings: (1) support for an association of hypofrontality with negative symptoms; (2) an indication that hippocampal more than lateral temporal dysfunction may lead to delusional symptoms; and (3) evidence suggesting parietal cortex and motor strip hyperactivity to be involved in disorganized thinking.

Based on the BPRS factor scores the patient sample was clustered into four subsyndrome clusters: delusional, negative symptoms, disorganized, and remitted. This subgrouping is consistent with earlier studies (Mundt, 1985; Schröder et al., 1992a) with negative symptoms not exclusively found in the negative symptoms cluster, but also present in the delusional patients. The co-occurrence of positive (delusional) and negative symptoms in the delusional cluster is in line with other studies (Maurer and Häfner, 1991; Rosen et al., 1984) that found the two psychopathological dimensions to be interrelated and refers to the distinction of primary negative symptoms (characteristic for the deficit state) versus secondary (reflecting a withdrawal due to persisting delusional symptoms) drawn by Carpenter (1992). The disorganized subsyndrome cluster patients scored highest on the disorganized factor and showed a considerable delusional symptomatology but hardly any negative symptoms. These findings confirm the view of Arndt and coworkers (1991) that the introduction of the disorganized subsyndrome may lead to a further differentiation of the positive domain into two subsyndromes rather than adding a third, independent dimension to the positive-negative dichotomy.

The finding of an association between delusional ideation and a decreased activity in the hippocampus is in accordance with Liddle et al. (1992). Magnetic resonance imaging (Bogarts et al., 1990; Breier et al., 1992; Suddath et al., 1990) and postmortem studies (Falkai et al., 1986) have revealed substantial evidence that the hippocampus is of importance in the pathogenesis of schizophrenic symptoms, but these studies have not assessed individual symptoms. This may explain that to a variable degree reduced hippocampal activity was observed in all schizophrenic clusters when compared with the healthy controls.

The cluster negative symptoms was characterized by a pronounced hypofrontality when compared with the cluster disorganized and the healthy controls. According to recent reviews (Andreasen et al., 1992; Buchsbaum, 1990), hypofrontality is a consistent PET and cerebral blood flow finding in schizophrenia and indicates a disturbed frontal lobe function. Further studies demonstrate that hypofrontality is not restricted to schizophrenia, but may be also observed in depressive states (Buchsbaum et al., 1984; Baxter et al., 1985, Schröder et al., 1989). Thus, one may conclude that hypofrontality is not specific for schizophrenia but may be associated with negative symptoms such as inactivity or decreased expression of affect. Evidence supporting this hypothesis and supporting the validity of our factor structure is derived from imaging studies on schizophrenic patients (Liddle et al., 1992; Volkow et al., 1987; Andreasen et al., 1992, Wolkin et al., 1992, Kaplan et al., 1993, Siegel et al., 1993).

The negative symptoms cluster also had high values on the factor left temporal cortex. This is consistent with Weinberger (1991) who supposed changes of the temporal activity to contribute to frontal abnormalities through the anteromedial temporal–prefrontal connectivity.

In addition to reflecting hypofrontality and hippocampal deactivation, the clusters negative symptoms and delusional shared a significantly reduced activity on the factor anterior cingulum and medial frontal gyrus. Andreasen et al. (1992), who investigated regional cerebral blood flow in 36 schizophrenic patients under a sequential planning and a control task, found medial frontal lobe impairment to be associated with negative symptoms; Tamminga et al. (1992) reported glucose metabolism in the anterior cingulum region to be reduced under partial sensory deprivation in deficit (negative symptoms) and non-deficit (delusional) patients. The anterior cingulum and medial frontal gyrus may be roughly assessed by measuring the width of the adjacent frontal interhemispheric fis-

sure which was significantly enlarged in delusional and negative symptoms patients when compared to patients with a disorganized symptomatology and patients with a remitting course of the disorder (Schröder et al., 1992a).

The cluster disorganized presented with the highest activity value on the factor parietal cortex and motor strip. This is consistent with the preponderance of thought disorders found in the disorganized cluster which are associated with neurological soft signs (Schröder et al., 1992b; Liddle, 1987b; Torrey, 1980). Evidence supporting this hypothesis comes from a regional cerebral blood flow (rCBF) study on 29 schizophrenic patients and eight healthy controls: in the patients with prominent positive symptoms, Günther et al. (1991) found a diffuse bilateral rCBF hyperactivation in the primary motor areas and precentral cortical regions under motor activation when compared to a non-reactivity in the patients with a predominance of negative symptoms. The low values on the factor corpus callosum found in the disorganized cluster may suggest changes of interhemispheric transmission which could account for delusions of control, hallucinations, and other positive symptoms (Nasrallah, 1985).

An association between disorganization and frontal lobe dysfunction reported by Liddle et al. (1992) was not found. This discrepancy might be due to the fact that Liddle and coworkers studied medicated patients and did not control the psychological state during the examination with a task. Furthermore, evidence from neuropsychological studies on the association between disorganization and frontal lobe functioning is equivocal (Liddle, 1987; Brown and White, 1992).

The differences in glucose metabolic rate between the various subsyndrome groups do not appear to be affected by the overall severity of illness. Significant correlations between the severity of illness and any of the factor scores were not found; moreover, while presenting with minimal symptomatology, the cluster remitted took various positions on the factors when compared to the other patients' cluster and the controls. This underlines that the activity differences are not merely a function of the overall severity of illness, but are rather due to psychopathological differences between the clusters.

Little is known about the temporal stability of the subsyndromes: while Kulhara and Chandiramani (1990) found the subsyndromes to remain stable over a period of 18 to 30 months, in the present study duration of illness differed between the clusters with the negative symptoms cluster being ill for the longest period (9.53 years). Following Kraepelin (1908), some studies suggest that the subsyndromes might represent different stages of the disease, with delusional and disorganized symptoms in the early phases and negative symptoms occurring in the defect state (Häfner and Maurer, 1991; McGlashan and Fenton, 1992). The duration of illness was significantly correlated with the factors thalamus and hypofrontality. Alternatively, early onset and pronounced hypofrontality may reflect a certain vulnerability towards the negative subsyndrome; thus, in a cross-sectional study they would have the longest duration.

The clusters characterized in our study may either represent distinct entities or individuals differing on continuous dimensions found in all of schizophrenia. None of the studies reporting similar factor analytic approaches gives a definitive answer (Arndt et al., 1991; Liddle, 1987, Peralta et al., 1992). From the observation that a patient can have symptoms from more than one subsyndrome, Liddle (1987) inferred that the subsyndromes 'do not represent distinct types of schizophrenia, but instead reflect discrete pathological processes occurring within a single disease.' The temporal stability of PET findings and subsyndrome assessments will be helpful in addressing this question.

According to our findings, the three subsyndromes of chronic schizophrenia deviate from each other with regard to the activities in the frontal and temporal lobe, the corpus callosum and parietal cortex and motor strip. When compared with the healthy controls, these findings were observed among all schizophrenic clusters, but to a different extent. Thus, single brain sites specific for one particular psychopathological syndrome could not be identified. More subtle changes may be recorded by combining morphological and functional imaging methods, resulting in a more precise

differentiation of the subsyndromes. However, the characterization of the subsyndromes does not entirely depend upon the sensitivity of the imaging methods, but also on the specificity of the psychopathological subsyndromes as they relate to cerebral changes. Contemporary neurophysiological approaches hypothesize that brain function relies on both, functional specialization and highly integrative functioning circuits (Volkow and Tancredi, 1991): different symptoms may therefore correspond to one particular localization; and at the same time one symptom may relate to several sites within the same functional system. An adequate strategy to elucidate this dilemma may be to investigate the same patients under varying conditions, such as different neuropsychological probes or psychopharmacological challenges (Buchsbaum et al., 1992) or to test circuitry models, such as proposed by Bunney (1990) and Carlsson and Carlsson (1990).

5. Conclusions

In conclusion, our study supports the clinical differentiation of three subsyndromes in chronic schizophrenia. While the delusional and the negative symptoms subsyndrome differ with regard to hypofrontality and hippocampal activity, both share a diminished activity in the anterior cingulum and medial frontal gyrus. The disorganized subsyndrome is characterized by an overactivity in the parietal cortex and motor strip and hardly shows any hypofrontality. The subsyndromes do not relate to the distinction of several independent subtypes of schizophrenia, but conform instead with the concept of one schizophrenia which shows different patterns of cerebral activation.

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