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Patterns of cortical activity in schizophrenia

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SYNOPSIS Eighty-three patients with schizophrenia and 47 healthy controls received positron emission tomography (PET) with 18F-2-deoxyglucose uptake while they were executing the Continuous Performance Test (CPT). The entire cortex was divided into 16 regions of interest in each hemisphere, four in each lobe of the brain, and data from corresponding right and left hemispheric regions were averaged. Data from the schizophrenic patients were subjected to a factor analysis, which revealed five factors that explained 80% of the common variance. According to their content, the factors were identified and labelled 'parietal cortex and motor strip', 'associative areas', 'temporal cortex', 'hypofrontality' (which included midfrontal and occipital areas) and 'frontal cortex'. Hemispheric asymmetry was only confirmed for the temporal cortex. Factor weights obtained in the schizophrenic group were applied to the metabolic data of the healthy controls and factor scales computed. Schizophrenics were significantly more hypofrontal than the controls, with higher values on the 'parietal cortex and motor strip' factor and a trend towards higher values in the temporal cortex. A canonical discriminant analysis confirmed that the 'hypofrontality' and 'parietal cortex and motor strip' factors accurately separated the schizophrenic group from the healthy controls. Hemispheric asymmetry was only confirmed for the temporal lobe. Significantly higher factor scores for the left temporal lobe in schizophrenics than in normals were obtained when calculated for the right and left hemisphere separately. Taken together, our results confirm the importance of hypofrontality as a pattern of cortical metabolic rate and point to the potential importance of parietal and motor strip function in schizophrenia.

INTRODUCTION

Kraepelin (1913), in conceptualizing 'dementia praecox' in the 8th edition of his textbook, distinguished between comprehension and attention. While the former remained unimpaired in most cases, disordered attention was one of the characteristics of the disorder. Two attentional tasks known to show deficits in schizophrenia, the Continuous Performance Test (Nuechterlein, 1983; Cornblatt *et al.* 1988, 1989) and the Wisconsin Card Sort Test (Weinberger *et al.* 1988), appear to enhance metabolism and cerebral blood flow in the frontal lobe in normal subjects but not in schizophrenics (Buchsbaum *et al.* 1984, 1990, 1992; Weinberger *et al.* 1988). These results have suggested a frontally mediated attentional dysfunction in schizophrenia (see review by Buchsbaum *et al.* 1990) and are consistent with the original finding by Ingvar & Franzen (1974) of hypofrontality. Ingvar & Franzen reported values for cerebral blood flow based on the ratio of the frontal to occipital lobe; this suggested some abnormality in the global pattern of cortical organization. Some findings with positron emission tomography (PET) have suggested actual hyperoccipitality in schizophrenics (Buchsbaum *et al.* 1982). Thus, it is not entirely clear to what extent the observed deficit is restricted to the frontal lobe or may reflect an imbalanced relationship of the frontal lobe to posterior regions. An additional difficulty in localizing the deficit is related to the technique of averaging functional information across large areas of the frontal lobe. Both Ingvar & Franzen (1974) and Weinberger *et al.* (1988), while obtaining data on cerebral blood flow from many detectors, have arbitrarily combined data from large cortical regions. While this is one

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strategy to minimize problems with multiple regional statistical comparisons and attendant Type I error, it neither takes into account the potential heterogeneity of the front lobe and posterior cortical regions nor considers the interconnective nature of cortical organization, as would factor analytic approaches (Volkow *et al.* 1986; Volkow & Tancredi, 1991). Small sample sizes have prevented the application of factor analysis to the cortical surface as a rigorous solution to this problem. In this study, we attempted to minimize Type I errors by the use of multivariate techniques to examine the interrelationships of cortical areas in patients with schizophrenia.

METHOD

Subjects

Eighty-three patients with schizophrenia (7 women, 76 men, mean age ± S.D. = 30·4 ± 7·9, mean age of onset 23·9 ± 7·3, mean duration of illness 6·6 ± 5·6 years) were recruited from the clinical and research programmes of the University of California at Irvine (UCI), Los Angeles (UCLA) and San Diego (UCSD). All but seven patients were right-handed. Patients had not received psychoactive medication for at least 30 days.

Particular care was taken to exclude patients with any history of neurological disorders or substance abuse. Psychiatric assessments of the patients were carried out in the week before the PET examination. The clinical diagnosis was confirmed using a version of the Present State Examination (Wing *et al.* 1974) that was modified to assess DSM-III-R criteria for schizophrenia. The Brief Psychiatric Rating Scale (BPRS; Overall & Gorham, 1962; Lukoff *et al.* 1986) was used to assess psychopathology; the mean ± S.D. BPRS score was 43·8 ± 12·5.

Forty-seven right-handed volunteers (17 women, 30 men) served as a control group (mean age ± S.D. = 30·2 + 9·7 years). Control subjects were screened for health just as the patients were, by history, physical examination and laboratory testing. The BPRS was not used.

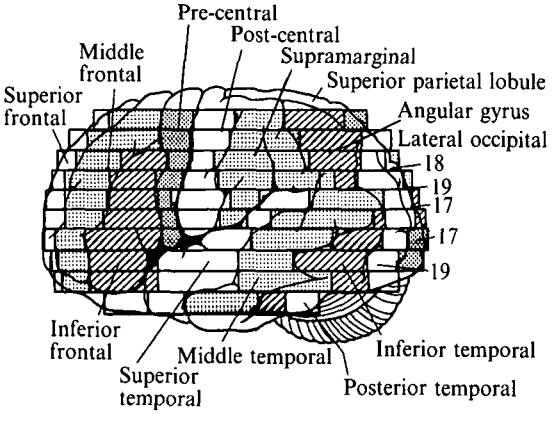

FIG. 1. Key figure for cortical areas. A digitized atlas was used to create stereotaxic analysis. Each gyral division marked in the atlas was identified on each of 10 slices from the top to the bottom of the brain. Percentages of brain perimeter distance from the most anterior point on the circumference were calculated for anterior and posterior limits of each cortical area. These percentages were then applied to each individual's PET scan (Siegel *et al.* 1992).

Measures

Continuous Performance Test

All subjects executed the degraded stimulus Continuous Performance Test (CPT; Nuechterlein *et al.* 1983) during the period for the uptake of 18F-2-deoxyglucose. Single digits (0–9) were presented for 40 ms at a rate of one every 2 s on a 24 × 24 cm screen. Subjects were asked to press a button with their right hand every time a zero occurred. Subjects were instructed that it was equally important to respond to the target as it was to neglect the non-targets. Targets were presented randomly with a probability of occurrence of 0·25.

Positron Emission Tomography

Changes in regional brain activity were imaged as glucose metabolic rate using sterile, pyrogen-free 18F-2-deoxyglucose, prepared as described elsewhere (Buchsbaum *et al.* 1989).

To minimize head movement, an individually moulded, thermosetting plastic head holder was made for each subject. For the period of 18F-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 to allow blood to be sampled and another line 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. The left arm was extended through a slit in a black curtain 200 cm high, so as to screen blood sample activity. All subjects were instructed on the CPT task before the injection time and were given trials to ensure their comprehension of the

task. Two to 3 min before the 18F-2-deoxyglucose injection (4–5 mCi), the room lights were extinguished and visual stimuli were begun; the stimuli continued for 32–37 min after the injection. All subjects remained quiet and cooperative. After 18F-2-deoxyglucose uptake, the subjects were transferred to the adjacent scanning room. Ten planes (CTI NeuroECAT) at 10 increments and parallel to the canthomeatal (CM) line were done between 45 and 100 min after 18F-2-deoxyglucose injection. Scans were performed with both shadow and septa shields in, a configuration with measured in-plane resolution of 7·6 and 10·9 mm resolution in the *z*-dimension (axial). A calculated attenuation correction and a smoothing filter were used. The scanner was calibrated on each scan day with a cylindrical phantom, and compared with well-counter data.

Scan slice selection and processing

Scans were transferred to glucose metabolic rate as described elsewhere (Buchsbaum *et al.* 1989). Sixteen cortical regions of interest (Fig. 1) were measured in each hemisphere using our cortical peel technique (Buchsbaum *et al.* 1989, see Harris *et al.* 1991 for review). Regional glucose use was expressed as relative glucose metabolic rate (GMR), which is defined as the ratio of regional GMR to whole brain GMR. This was necessary because glucose metabolic rate in micromoles/100 g/min is very highly correlated across cortical areas and preliminary factor analyses showed only a single relatively uniformly weighted factor.

Data analysis

All statistical computations were performed using the Statistical Analysis System (SAS Institute, 1990) statistical package. First, the relative cortical metabolic activity for schizophrenic patients was investigated for underlying dimensions with principal component factor analysis with varimax rotation (SAS: Proc factor). In selecting the variables to enter to reduce the ratio for the number of variables to the number of observations, we computed the means of corresponding regions in the right and left hemispheres; this computation yielded 16 variables, four for each lobe of the brain. The number of factors retained was determined by analysing the scree plot and the possible clinical interpretation (Geider *et al.* 1982; Bernstein, 1988). The identified cortical factors, which represent patterns of cortical activity, allowed the construction of factor scales as recommended by Bernstein (1988) and Geider *et al.* (1982) and following the example of Volkow and coworkers (1986). Scores for each of the cortical factors were calculated for each individual patient and control by averaging the items weighing 0·50 or above in reference to each factor. This was done using the factor structure of the schizophrenics because we expected that the greater variability in hypofrontality in schizophrenic patients would lead to a better definition of the structure of the factors. We were concerned that in reducing the number of variables by averaging the left and right hemisphere we might have increased factor structure stability at the expense of the possible underlying dimension of lateralization. Therefore, we decided to calculate two factor analyses, the first on the basis of 16 bihemispheric variables to explore the relative cortical metabolic activity for underlying subdimensions, i.e. patterns of cortical activity; the second, 'confirmatory', analysis on basis of the original 32 variables from the left and the right hemisphere to control the results for possible lateralization effects.

Subsequently, the factor scale values of schizophrenic patients and the healthy controls were compared. Finally, a canonical discriminant analysis (SAS: Proc discrim) was performed. This procedure was chosen because it identifies those variables that explain most of the variance found between both groups. In a last step, we explored possible lateralization effects using the factor scales resulting from the 16 variable factor analysis separately recalculated for each hemisphere; the resulting values from normals and schizophrenics were compared. Since the control group comprised a larger proportion of females than the patients' sample, we compared the factor scale values between female and male controls to examine possible sex differences.

RESULTS

Cortical metabolic patterns

Following the inspection of the scree plot and the possible neuroanatomical interpretation, we selected the five-factor solution with 80% of the common variance (Table 1).

Table 1. *Factor loadings for the cortical surface using varimax rotation*

	Factor 1	Factor 2	Factor 3	Factor 4	Factor 5
Pre-central gyrus	0·8801	0·1872	−0·2035	−0·0822	0·0853
Post-central gyrus	0·9142	0·0489	−0·1238	0·0715	−0·0873
Supramarginal gyrus	0·6756	0·4598	−0·2544	−0·2536	−0·1745
Angular gyrus	0·3898	0·7510	−0·2265	−0·3172	−0·0479
Superior parietal gyrus	0·0827	0·7828	−0·3614	−0·0501	0·1548
Brodmann's area 19	0·1916	0·7274	0·2900	0·3528	−0·1665
Brodmann's area 17	0·0831	0·8060	−0·3524	0·1511	0·0472
Middle temporal gyrus	−0·3021	−0·2578	0·7852	0·1487	0·1762
Inferior temporal gyrus	−0·2283	−0·1203	0·8948	0·1727	−0·0735
Posterior temporal region	−0·0976	−0·2133	0·5827	0·0825	−0·2432
Middle frontal gyrus	0·4500	0·2591	−0·3224	−0·5705	0·3984
Brodmann's area 17	0·0501	0·0792	0·0114	0·9231	−0·1052
Brodmann's area 18	−0·2425	0·0601	0·3406	0·7174	−0·2407
Superior frontal gyrus	−0·2134	0·0680	−0·2808	−0·3353	0·7053
Inferior frontal gyrus	0·0162	−0·0455	0·0479	−0·1142	0·9200
Eigenvalue	2·99	2·97	2·69	2·30	1·90
Percentage of variance*	18·7	18·5	16·8	14·4	11·9

* After varimax rotation.

Table 2. *Means and standard deviations of the factor scales in the schizophrenic patients and the healthy controls*

	Factors				
	Parietal motor strip	Associative areas	Temporal cortex	Hypofrontality	Frontal cortex
Schizophrenics					
Mean	1·18	1·13	0·92	0·36	1·11
S.D.	0·08	0·09	0·08	0·08	0·05
Healthy controls					
Mean	1·15	1·12	0·90	0·33	1·11
S.D.	0·09	0·11	0·05	0·06	0·04
Univariate *P*	0·03	0·66	0·07	0·03	0·97

Table 3. *Rotated standardized discriminant function coefficients*

	Parietal motor strip	Associative areas	Temporal cortex	Hypo-frontality	Frontal cortex
Discriminant function	1·101	−0·179	0·506	0·843	0·517

The measures of the relative GMR in the pre-central motor cortex and the parietal regions (pre-central gyrus region, post-central gyrus region and supramarginal gyrus region) showed high loadings on Factor 1. This factor was labelled 'parietal cortex and motor strip'. Factor 2 was labelled 'associative areas', as it encompassed the angular gyrus, superior parietal gyrus, and areas 17 and 19 of the occipital lobe. The middle temporal gyrus, inferior temporal gyrus, and posterior temporal region made up Factor 3, which was labelled 'temporal cortex'. Factor 4, which had positive weights for occipital areas 18 and 17, and negative weights for the mid-frontal region, was labelled 'hypofrontality'. Factor 5 was labelled 'frontal cortex' as it consisted of the activity measured in the superior frontal and inferior frontal region. The measure of the superior temporal gyrus did not show any preferential loadings. Table 2 presents the mean factor scale values for the two groups.

The patients with schizophrenia had significantly higher scores on Factor 1 (parietal cortex

Table 4. *Means and standard deviations of the factor scales separately calculated for each hemisphere*

	Parietal motor strip		Associative areas		Temporal cortex		Hypofrontality		Frontal cortex	
	Left	Right	Left	Right	Left	Right	Left	Right	Left	Right
Schizophrenic patients										
Mean	1·17	1·18	1·11	1·14	0·91	0·92	0·36	0·36	1·11	1·10
S.D.	0·09	0·07	0·09	0·1	0·07	0·08	0·08	0·07	0·05	0·05
Controls										
Mean	1·14	1·15	1·10	1·14	0·88	0·91	0·33	0·33	1·11	1·11
S.D.	0·09	0·08	0·11	0·11	0·05	0·06	0·06	0·06	0·04	0·04
Univariate *P*	0·03	0·05	0·41	0·97	0·02	0·25	0·05	0·04	0·46	0·50

and motor strip) and on Factor 4 (hypofrontality). Scores in the groups did not differ for the 'frontal cortex' factor. Neither the CPT, BPRS total score nor any single BPRS item was significantly correlated with any of the factor scale dimensions. No significant differences between men and women were found on factor scale values.

Discriminant analysis

A canonical discriminant analysis, which used the five-factor scale values for each subject, was carried out between the patients and the controls. The discriminant function (Table 3) had the highest standardized canonical coefficients for Factors 1 and 4. The group mean on the canonical discriminant function was −0·58 for the controls and 0·33 for the patients. The discriminant function proved to be highly significant ($P < 0·0005$) and attained a correct reclassification of 69% of the entire sample. The function identified 70/83 (84·3%; good sensitivity) of schizophrenics correctly but only 19/47 (40·4%; modest specificity) of controls correctly.

To explore possible lateralization effects, we used the factor weights to calculate new factor scales on each hemisphere separately, thus resulting in 10 scores, five for each hemisphere (Table 4). This produced similar results, with Factors 1 and 4 significant for both hemispheres. The only addition was Factor 3, the temporal lobe factor, which was significantly higher on the left in schizophrenics than in controls. Examination of the factor analysis entering 32 variables, 16 in each hemisphere confirmed this structure. Right and left side cortical areas usually loaded on the same factor except in the temporal lobe where left-sided areas appeared on one factor and right-sided areas on a second. This 32 variable factor analysis is available to readers on request.

DISCUSSION

Our analyses provide two main findings: (1) support for an anteroposterior pattern of cortical organization; and (2) a left temporal hyperactivity that distinguished schizophrenics from normal controls. Cortical activity in schizophrenia during a vigilance task was differentiated into five dimensions of cortical activity, with 'hypofrontality' and 'parietal cortex and motor strip' significantly differentiating between schizophrenic patients and healthy controls. Secondly, the bilateral temporal factor did not differ between patients and controls, but when analysis was restricted to the left hemisphere, temporal increases consistent with our earlier study (DeLisi *et al.* 1989) emerged. Thus, deviant patterns of activity, rather than only abnormal localized deficit, seem to characterize schizophrenia.

Our results are not entirely dissimilar to earlier results reported by Volkow *et al.* (1986), who investigated cortical (four regions of interest in each hemisphere), basal ganglia, thalamic and whole brain activity in a group of 18 schizophrenic patients and 12 controls. Factor analysis revealed four factors: frontal, left/right hemisphere (mainly temporal lobe), occipital and subcortical. While the two studies differ on many features, they agree on a relatively

decreased frontal activity and the importance of lateralization in temporal lobe loadings.

There are three sources of variation that are important in determining the correlations between cortical regions and the factor structure observed. Correlations may be caused by neuronal connections between different cortical areas (see Horwitz *et al.* 1991 for additional discussion); these circuits may be: (1) tonically active; (2) activated during particular clinical states or in different diagnostic subgroups; or (3) activated by the CPT. Nevertheless, these sources of variation show the possibility that different cortical areas that appear on the same factor act or react in a similar manner thus establishing a systematic covariance between them. Since we controlled attention by having all subjects do the CPT, thus reducing the attention system's variation, it is not entirely surprising that CPT scores did not correlate with the factors we obtained. The CPT task was used to guard against the variability that inevitably occurs when subjects are studied in an uncontrolled so-called 'resting' state. It was not our intention to identify the components of 'CPT activation' *per se*. Rather, our factor analysis approach was aimed at contrasting patterns of brain activity in the schizophrenic patient group with those in a control group. In our PET studies of over 100 patients we have found general patterns of regional metabolic activity that characterize patients with schizophrenia regardless of whether patients are tested in the resting state (Buchsbaum *et al.* 1982), while receiving electric shocks (Buchsbaum *et al.* 1984), or while performing the continuous performance test (Buchsbaum *et al.* 1990). Similarly diverse conditions were used in the studies of Ingvar & Franzen (1974) and Weinberger *et al.* (1988). The use of the CPT, a task with demonstrated salience to the genetic vulnerability to develop schizophrenia, serves to heighten the differences between normal and schizophrenic groups, but does not completely alter the differential patterns of metabolic activity observed. Lastly, task performance may not have a linear relationship with glucose metabolic rate (Haier *et al.* 1991).

Neuronal connectivity is not the only source from which correlation between areas can arise; they merely reflect the finding that GMR in two regions shows a linear relationship across subjects. Thus, a correlation between the thalamus and frontal lobe implies that there are subjects who have high values in both areas as well as subjects who have low values in each area. This has been taken to imply that the regions are 'functionally coupled' (Horwitz 1991). This variance could arise from a continuous individual difference such as severity of illness and thus appear in the patient, but not in the normal group. It could also arise from heterogeneous diagnostic typology, with one diagnostic subgroup having low values in both areas and another diagnostic subgroup characterized by a different pathophysiology having normal values in both areas. Thus, if a virus or genetic deficit struck a particular type of brain cell, which occurs at different densities in different brain regions in a fraction of patients with schizophrenia, it could produce correlations between metabolic rate in these regions. An alternative method of studying the natural relationships between structures is to measure within-subject variation, which can only be assessed by multiple scans in conditions that cause regional activation varying on a linear continuum. Nevertheless, even if correlations arise from a diagnostic typology the correlation pattern reflects regional similarities and a pattern of cerebral change, if not connectivity change.

Our factor analysis may also suggest that attention is not a unitary or highly localized phenomenon, but rather that it involves different cortical areas at one time: neuropsychological approaches suggest a differentiation of attention into such components as focusing on a target, sustaining the focus, encoding stimulus patterns and shifting the focus (Mirsky, 1987). This phenomenological differentiation was confirmed using a factor analysis of the attentional performance in a group of 86 healthy subjects (Mirsky, 1987). Four factors explaining 71% of the common variance emerged: 'perceptual-motor speed', 'vigilance', 'numerical-mnemonic', and 'flexibility'. These factors were related to focusing, sustaining, encoding and shifting attention, respectively. This differentiation is not dissimilar to the factor structure found in our study but tends to suggest that the CPT score, which reflects all of these factors, would not correlate significantly with a single factor.

The first factor 'parietal cortex and motor strip' appeared to be heavily weighted in the

pre-central, post-central and supramarginal gyri, all of which share a sensory or motor function. This is consistent with the phenomenological theories suggesting that motor systems not only control action but also participate in perception and anticipation of the environment (Kraus, 1974). The significant correlation between performance on the CPT and motor disturbances in patients with either schizophrenia or affective psychosis (Walker & Green, 1982) also suggests this. Schroeder *et al.* (1993) reported that sustained attention, which was assessed with a measure not dissimilar to the CPT, covaried with neurological soft signs that included both minor motor and sensory disturbances, a finding that is also consistent with the current factor structure. These neurological soft signs had previously been shown to appear with greater frequency in patients with schizophrenia than in healthy controls (Schroeder *et al.* 1992). Guenther *et al.* (1991) who investigated regional cerebral blood flow in 32 schizophrenic patients and 8 healthy controls found a bilateral overactivity in the precentral gyrus under motor stimulation in the Type I patients. However, it is unclear whether this dysfunction is caused by a primary motor or sensory deficit, or whether it reflects a compensatory effort to overcome disturbances that are located elsewhere (Heinrichs & Buchanan, 1988). In our initial analysis of 13 of these patients (Buchsbaum *et al.* 1990), we also noted increased glucose utilization in the parietal region in schizophrenic patients, and suggested that this might represent a shift of activity from the more appropriate, efficient or capable areas of the frontal lobe to alternate areas. These increases could be associated with inefficient or less capable function or with less rapid learning of the task (Haier *et al.* 1991).

The second factor 'associative areas' encompassed the angular and the superior parietal gyrus, visual association area 19, and primary visual area 17 as well. The association between attention and the parietal gyrus mentioned above is supported by Petersen *et al.* (1989), who found an increased regional cerebral blood flow in the angular and posterior parts of the parietal cortex in healthy subjects under a vigilance task. Summarizing this and other findings, LaBerge (1990) suggests that the parietal lobe may assist the processing of any object occurring in the visual field and that it may play a particular role in fast processing and accurate detection or identification. Our data could be taken to suggest that this aspect of attention is not the primary deficit in schizophrenia.

The function of the temporal cortex in attention (Factor 3) has been summarized as providing the memory capacities needed or serving as a multimodal sensory convergence area (Pandya & Yeterian, 1985; Mirsky, 1987). As a bilateral factor, it provided a very small contribution to the discriminant function separating normal subjects and patients. However, since DeLisi and coworkers (1989) found that schizophrenic patients showed a significantly greater left than right metabolic rate in the anterior temporal lobe, we explored the left and right sides separately. Thus, our current results are consistent with the earlier report, with higher left temporal metabolism being confirmed in the patient group. Our factor analyses indicated that lateralization appears much more important for the temporal than frontal or parietal systems.

The fourth factor was labelled 'hypofrontality' as it included two positively weighted occipital cortical areas and the negatively weighted middle frontal gyrus. First reported in 1974 by Ingvar & Franzen, a decreased frontal/occipital blood flow ratio has been confirmed in many, but not all, PET and blood flow studies of schizophrenia (for review, see Buchsbaum, 1990). The identification of the 'hypofrontality' factor provides evidence that this ratio is not just arbitrarily defined but represents a functional organizational pattern of the cortex in schizophrenia. It also suggests that analytical approaches that involve both the frontal and occipital cortex, as ratios or in multivariate approaches, may be more powerful statistically in demonstrating group differences. EEG studies (Hoffman *et al.* 1991) have also demonstrated reduced frontal/occipital coherence, consistent with this anteroposterior relationship.

The fifth factor 'frontal cortex' consisted of the interior and superior frontal areas. In the attentional process, the frontal lobe is of crucial importance to maintain planning and executive function as well as shifts of attentional focus (Benson & Stuss, 1986). Factor 5, loading frontal regions alone, failed to show normal/schizophrenic differences. In contrast, Factor 4,

loading both frontal and occipital areas, showed differences between normals and schizophrenics. This suggests that attentional tasks that require frontal and occipital coordination, or tasks for which there are alternate strategies that involve occipital or parietal processing, may be especially useful in studies of schizophrenia. It may also be that the CPT fails to activate attentional systems located entirely within the frontal cortex such as short-term memory. Systematic assessment of major white matter regions (typically omitted in quantitative studies) such as the fronto-occipital fasciculus with MRI measurement may also be productive in understanding these inter-regional cortical relationships.

REFERENCES

Benson, D. F. & Stuss, D. T. (1986). *The Frontal Lobes*. Raven Press: New York.

Bernstein, I. H. (1988). *Applied Multivariate Analysis*. Springer-Verlag: New York.

Buchsbaum, M. S. (1990). The frontal lobes, basal ganglia and temporal lobes as sites for schizophrenia. *Schizophrenia Bulletin* **16**, 379–389.

Buchsbaum, M. S., Ingvar, D. H., Kessler, R., Waters, R. N., Cappelletti, J., van Kammen, D. P., King, A. C., Johnson, J. L., Manning, R. G., Flynn, R. W., Mann, L. S., Bunney, W. E., Jr. & Sokoloff, L. (1982). Cerebral glucography with positron emission tomography. *Archives of General Psychiatry* **39**, 251–259.

Buchsbaum, M. S., Holcomb, H. H., DeLisi, L. E., Cappelletti, J., King, A. C., Johnson, J., Hazlett, E., Post, R. M., Morihisa, J., Carpenter, W., Cohen, R., Pickar, D. & Kessler, R. (1984). Anteroposterior gradients in schizophrenia and affective disorders. *Archives of General Psychiatry* **41**, 1159–1166.

Buchsbaum, M. S., Gillin, J. C., Wu, J., Hazlett, E., Sicotte, N. & DuPont, R. M. (1989). Regional cerebral glucose metabolic rate in human sleep assessed by positron emission tomography. *Life Sciences* **45**, 1349–1356.

Buchsbaum, M. S., Nuechterlein, K. H., Haier, R. J., Wu, J., Sicotte, N., Hazlett, E., Asarnow, R., Potkin, S. & Guich, S. (1990). Glucose metabolic rate in normals and schizophrenics during the continuous performance test assessed by positron tomography. *British Journal of Psychiatry* **156**, 216–227.

Buchsbaum, M. S., Haier, R. J., Potkin, S. G., Nuechterlein, K., Bracha, S., Katz, M., Lohr, J., Wu, J., Lottenberg, S., Jerabek, P. A., Trenary, M., Tafalla, R., Reynolds, C. & Bunney, W. E. (1992). Fronto-striatal disorder of cerebral metabolism in never-medicated schizophrenics. *Archives of General Psychiatry* **49**, 935–942.

Cornblatt, B. A., Risch, N. J., Faris, G., Friedman, D. & Erlenmeyer-Kimling, L. (1988). The Continuous Performance Test, Identical Pairs Version (CPT-IP): new findings about sustained attention in normal families. *Psychiatry Research* **26**, 223–238.

Cornblatt, B. A., Lenzenweger, M. F. & Erlenmeyer-Kimling, L. (1989). The Continuous Performance Test, Identical Pairs Version (CPT-IP). II. Contrasting attentional profiles in schizophrenic and depressed patients. *Psychiatry Research* **29**, 65–86.

DeLisi, L. E., Buchsbaum, M. S., Holcomb, H. H., Langston, K. C., King, A. C., Kessler, R., Pickar, D., Carpenter, W. T. Jr., Morihisa, J. M., Margolin, R. & Weinberger, D. R. (1989). Increased temporal lobe glucose use in chronic schizophrenic patients. *Biological Psychiatry* **25**, 835–851.

Geider, F. J., Rogge, K.-E. & Schaaf, H. P. (1982). *Einstieg in die Faktorenanalyse*. Quelle & Mayer: Heidelberg.

Guenther, W., Petsch, R., Steinberg, R., Moser, E., Streck, P., Heller, H., Kurtz, G. & Hippius, H. (1991). Brain dysfunction during motor activation and corpus callosum alterations in schizophrenia measured by cerebral blood flow and magnetic resonance imaging. *Biological Psychiatry* **29**, 535–555.

Haier, R. J., Siegel, B. V., MacLachlan, A., Soderling, E., Lottenberg, S. & Buchsbaum, M. S. (1991). Regional glucose metabolic changes after learning a complex visuospatial motor task: a positron emission tomographic study. *Brain Research* **570**, 134–143.

Harris, G. J., Links, J. M., Pearlson, G. D. & Camargo, E. E. (1991). Cortical circumferential profile of SPECT cerebral perfusion in Alzheimer's disease. *Psychiatry Research: Neuroimaging* **40**, 167–180.

Heinrichs, D. W. & Buchanan, R. W. (1988). Significance and meaning of neurological signs in schizophrenia. *American Journal of Psychiatry* **145**, 11–18.

Hoffman, R. E., Buchsbaum, M. S., Escobar, M. D., Makuch, R. W., Nuechterlein, K. H. & Guich, S. M. (1991). EEG coherence of prefrontal areas in normal and schizophrenic males during perceptual activation. *Journal of Neuropsychiatry and Clinical Neurosciences* **3**, 169–175.

Horwitz, B., Swedo, S. E., Grady, C. L., Pietrini, P., Schapiro, M. B., Rapoport, J. L. & Rapoport, S. I. (1991). Cerebral metabolic pattern in obsessive–compulsive disorder: altered intercorrelations between regional rates of glucose utilization. *Psychiatry Research: Neuroimaging* **40**, 221–237.

Ingvar, D. H. & Franzen, G. 91974). Abnormalities of cerebral blood flow distribution in patients with chronic schizophrenia. *Acta Psychiatrica Scandinavica* **50**, 425–462.

Kraepelin, E. (1913). *Psychiatrie. Ein Lehrbuch für Studierende und Ärzte*. Band III, Teil 2. 8. Auflage. Johann Ambrosius Barth Verlag: Leipzig.

Kraus, A. (1974). Stoerungen der Wahrnehmung und des Leiberlebens beim Parkinsonismus. Klinischer Beitrag zur Theorie der Einheit von Wahrnehmen und Bewegung. *Nervenarzt* **45**, 639–646.

LaBerge, D. (1994). Thalamic and cortical mechanisms of attention suggested by recent positron emission tomographic experiments. *Journal of Cognitive Neuroscience* **2**, 358–372.

Lukoff, D., Nuechterlein, K. H. & Ventura, J. (1986). Manual for expanded Brief Psychiatric Rating Scale (BPRS). *Schizophrenia Bulletin* **12**, 594–602.

Mirsky, A. F. (1987). Behavioral and psychophysiological markers of disordered attention. *Environmental Healthy Perspectives* **74**, 191–199.

Nuechterlein, K. H. (1983). Signal detection in vigilance tasks and behavioral attributes among offspring of schizophrenic mothers and among hyperactive children. *Journal of Abnormal Psychology* **92**, 4–28.

Nuechterlein, K. H., Parasuraman, R. & Jiang, Q. (1983). Visual sustained attention: image degradation produces rapid decrement over time. *Science* **220**, 327–329.

Overall, J. E. & Gorham, D. R. (1962). The Brief Psychiatric Rating Scale. *Psychological Reports* **10**, 799–812.

Pandya, D. N. & Yeterian, E. H. (1985). Architecture and connections of cortical association areas. In *Cerebral Cortex: Association and Auditory Cortices*, vol. 4 (ed. A. Peters and E. G. Jones), pp. 3–61. Plenum Press: New York.

Petersen, S. E., Corbetta, M., Miezin, F. M. & Dobmeyer, S. M. (1989). Selective attention modulates visual processing of form, color and velocity. III. Areas related to higher-order selective processes. *Journal of Neuroscience* **15**, 624.

SAS Institute. (1990). *SAS Language* (6th edn). SAS Institute: Raleigh, NC.

Schroeder, J., Niethammer, R., Geider, F.-J., Reitz, Ch., Binkert, M., Jauss, M. & Sauer, H. (1992). Neurological soft signs in schizophrenia. *Schizophrenia Research* **6**, 25–30.

Schroeder, J., Richter, P., Geider, F. J., Niethammer, R., Binkert, M., Rietz, Ch. & Sauer, H. (1993). Diskrete motorische und

sensorische Storungen in Akutverlauf endogener Psychosen. *Zeitschrift für klinische Psychologie, Psychopathologie und Psychotherapie* **41**, 190–206.

Siegel, B. V., Asarnow, R., Tanguay, P., Call, J. D., Abel, L., Ho, A., Lott, I. & Buchsbaum, M. S. (1992). Regional cerebral glucose metabolism and attention in adults with a history of childhood autism. *Journal of Neuropsychiatry and Clinical Neurosciences* **4**, 406–414.

Volkow, N. D. & Tancredi, L. R. (1991). Biological correlates of mental activity studies with PET. *American Journal of Psychiatry* **148**, 439–442.

Volkow, N. D., Brodie, J. D., Wolf, A. P., Gomez-Mont, F., Cancro, R., Van Gelder, P., Russell, J. A. G. & Overall, J. (1986). Brain organization in schizophrenia. *Journal of Cerebral Blood Flow and Metabolism* **6**, 441–446.

Walker, E. & Green, M. (1982). Motor proficiency and attentional-task performance by psychotic patients. *Journal of Abnormal Psychology* **91**, 261–268.

Weinberger, D. R., Berman, K. F. & Illowsky, B. P. (1988). Physiological dysfunction of dorsolateral prefrontal cortex in schizophrenia. *Archives of General Psychiatry* **45**, 609–615.

Wing, J. K., Cooper, J. E. & Sartorius, N. (1974). *Measurement and Classification of Psychiatric Symptoms.* Cambridge University Press: London.