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DYSFUNCTION IN A PREFRONTAL SUBSTRATE OF SUSTAINED ATTENTION IN SCHIZOPHRENIA

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Summary

Regional brain metabolism was measured in normal subjects and patients with schizophrenia while they performed an auditory discrimination task designed to emphasize sustained attention. A direct relationship was found in the normal subjects between metabolic rate in the middle prefrontal cortex and accuracy of performance. The metabolic rate in the middle prefrontal cortex of patients with schizophrenia, even those who performed as well as normals, was found to be significantly lower than normal and unrelated to performance. The findings point to a role of the mid-prefrontal region in sustained attention and to dysfunction of this region in schizophrenia.

Continuous performance tests have consistently been reported to demonstrate deficits in the maintenance of directed attention in schizophrenia (1-4). Because these deficits may lie closer to those primary defects presumed to be associated with genetic errors than the overt symptomatology of schizophrenia (5-7), we wanted to examine the functional localization of this ability in normal controls and in patients with schizophrenia.

Positron emission tomography (PET) studies with [18F]-2-fluoro-2-deoxy-D-glucose (FDG) allow for the evaluation of the anatomic substrate of mental abilities through the measurement of regional glucose metabolic rates during ongoing performances (8-10). Regional brain metabolism was measured by PET in patients with schizophrenia and normal control subjects during the performance of a 35-minute auditory discrimination task that was designed to 1) resemble other continuous performance tests, but which made use of auditory as opposed to visual stimuli to insure equivalent stimulus presentation to each subject, 2) allow for the evaluation of behavior during the actual period of metabolic measurement and 3) minimize the complexity of task requirements, e.g. perceptual processing and motor response, not directly related to maintainance of directed attention.Directed attention is fundamental to the performance of this task since the subject must maintain selective filtering of incoming stimuli so as to identify a target tone by pressing a hand-held manipulandum.

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Methods

Subjects: 27 healthy volunteers, 15 males and 12 females with a mean age of 32.9 years, s.d. = 12.2 years, participated in the study. Patients, 12 male and 4 female patients with a mean age of 27.5 years, s.d. = 6.6, met DSM III (American Psychiatric Association) criteria for schizophrenia as determined by the consensus of two psychiatrists. 7 patients were considered to be of the undifferentiated type, 7 of the paranoid type, 1 of the residual type and 1 of the disorganized hebephrenic type. The patients resided on research units and had not received neuroleptic medications for an average of 34 days (range 13-73, s.d. = 17.5; 1 patient had never received treatment) prior to study. The average duration of illness was estimated to be 8.0 ± 6.3 years with a range of 2 to 27 years. For the period just prior to their scan, the average 22-item Brief Psychiatric Rating Scale (BPRS) (11) total score was 58.7 ± 15.0. The average score ± s.d on the BPRS subscales was 9.94 ± 4.23 for thought disorder, 7.25 ± 4.00 for anxiety/depression, 6.63 ± 3.05 for hostility/suspiciousness and 7.01 ± 2.24 for withdrawal/retardation. The age and sex of the patients with schizophrenia did not statistically differ from those of the normal controls. Furthermore, analysis of the standardized regional glucose metabolic data demonstrated that neither the length of time that had elapsed from the time a patient had received his last dose of medication to the time of scan, i.e. 13 days to 73 days, nor the sex and age of the patients contributed significantly to the patient metabolic data.

Behavioral Task: The auditory continuous performance task (CPT) consisted of a random series of 500 hz tones of 1.0 second duration and 2.0 second inter-tone-interval, with an intensity of 67, 75, or 86 decibels, measured at the earphone-ear interface. The subject was instructed to press the hand-held response button when the lowest volume tone was detected. The task was presented in successive 5 minute blocks for 30 minutes following FDG injection. A total of 220 targets and 440 distractors were presented to each subject. To minimize learning contributions to the metabolic pattern, normals and schizophrenic patients were trained to a criterion of 18 of 20 correct identifications in this task in the hour preceding [18F]FDG injection. Subjects received scores for correct identifications of target tones (hits) and incorrect identification of distractors (false alarms).

PET Scan Procedure: Subjects, with eyes patched, began their auditory discrimination task several minutes prior to the injection of a 3-5 mCi dose of [18F]FDG and completed the task 35 min after injection. Arterialized venous blood samples were taken from the left arm for quantification of [18F]FDG uptake. Following the 35-min uptake period, subjects were placed in the scanner. Seven to eight slices were obtained from each subject starting from 80% of head height and proceeding in the caudal direction. Slices were parallel to the canthomeatal line (CM) and the interslice interval was 13 mm. Scans were performed with an Ortec ECAT II scanner of 1.75 cm. full width half-maximum resolution and used a calculated attenuation correction.

Data Analysis: Raw pixel values were converted to glucose metabolic rate in mg/100 g tissue/minute (12-14). For the extraction of regional glucose metabolic rates, 2.9 cm2 boxes were placed over the regions of interest in five standard planes; Plane A (9.1 cm above CM), B (7.8 cm above), C (6.5 cm above), D (5.2 cm above), E (3.9 cm above). Two independent raters who were unaware of the identity and diagnosis of the individual whose scan they were evaluating selected the planes for analysis and placed the boxes through neuroanatomical matching to a standard template (15)(See Fig. 1). Anatomical structures are judged as contained within these regions on the basis of the atlas of Matsui and Hirano (16). Global glucose metabolic rates refer to the

estimates of the average value for glucose metabolism obtained for all the gray matter rich areas of the brain sampled. Regional glucose metabolic rates refer to the average of standardized absolute glucose metabolic data obtained from specific areas of the cortex (See Fig. 1). The standardization procedure is designed to minimize the effects of individual variation in global glucose metabolism on regional comparisons by dividing an individual's glucose metabolic rate in a specific region by the individual's global glucose metabolic rate. The procedure is similar in principle to the "reference ratio" or "landscape method" (17). It is important to note that although standardization of metabolic rates was necessary in most instances to establish significance the size of the percent changes in absolute glucose metabolic rates in these same regions were always in the same direction and of the same or usually larger magnitude.

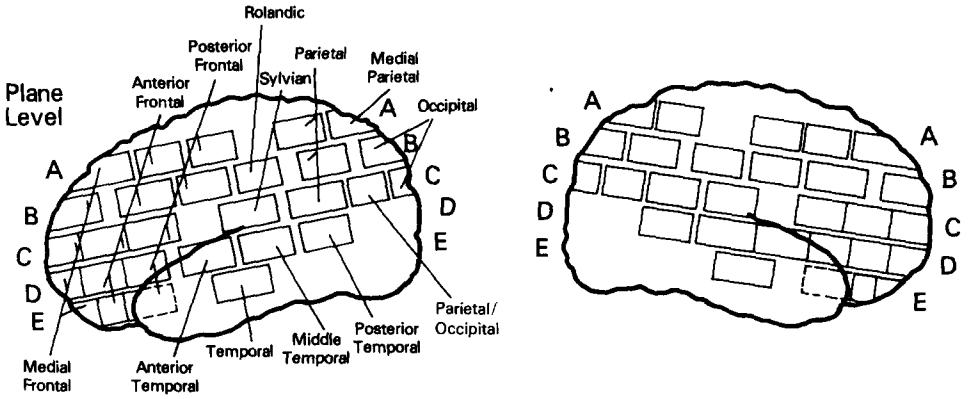

FIG. 1

Schematic representation of regions sampled in the left and right hemispheres. Regions labeled as medial, although sampled from the medial portion of the cortex, are represented as incomplete boxes on the lateral surface. The boxes outlined by dashed lines are sampled from the surface of the frontal cortex, medial to the temporal cortex.

Results

The schizophrenic patients (6.99 ± 1.06 mg glucose/100 gm of tissue/min) and the normal controls (7.04 ± 1.50 mg glucose/100 gm of tissue/min) did not differ in their global glucose metabolic rates. We then evaluated the glucose metabolic rates in 55 regions of the brain selected to maximize the quantitative localization of brain function on the basis of the resolution of our PET instrumentation (Fig. 1). Of the 55 regions examined, the only ones whose rates differed between the patients with schizophrenia and the normal controls by 2-tailed t-test were the medial parietal cortex ($p = 0.05$), the left anterior temporal cortex of the D plane ($p = 0.05$), and 5 regions within the mid-frontal cortex ($p = 0.05$ to $p = 0.001$).

To reduce the possibility of spurious differences arising from the large number of comparisons (Type I error), we deemed as reliable only those

TABLE I
REGIONAL GLUCOSE METABOLIC RATE DIFFERENCES
BETWEEN NORMAL CONTROLS AND HIGH AND LOW SCORING SCHIZOPHRENIC PATIENTS

Frontal Cortex

REGION	L. Posterior	L. Anterior	Medial	R. Anterior	R. Posterior
Plane					
A	+9.9* (-0.5)	+5.4 (+2.0)	+5.1 (+3.1)	+8.7* (+0.8)	+9.1** (+1.4)
B	+2.1 (+0.4)	+0.8 (-3.1)	+1.5 (-0.0)	-0.2 (-2.4)	+0.8 (+2.7)
C	-0.2 (+3.1)	-3.6 (-3.4)	-4.9 (-1.2)	-4.4 (-5.3+)	-3.5* (+1.4)
D	-6.4* (+0.2)	-7.2* (-7.7*)	-8.5+ (-7.8**)	-5.8* (-6.5**)	-9.0**(-1.7)
E	-2.2 (+7.2+)	+1.6 (-1.7)	-1.2 (-2.8)	+3.1 (-1.9)	-2.1 (+7.4+)

Temporal Cortex

	L. Posterior	L. Middle	L. Anterior	R. Anterior	R. Middle	R. Posterior
Plane						
D	-2.8 (-4.7)	-5.0 (+0.8)	-6.8* (-2.6)	-7.5* (-1.1)	-5.0 (+2.6)	-2.2 (-3.1)
E		-2.6 (+7.4*)			+1.4 (+5.0)	

The table is derived by subtracting the regional glucose metabolic rates of the frontal cortex of the normal control group (n = 27) from those of the HIGH (n = 7) and LOW (n = 9) scoring schizophrenic patient subgroups and multiplying by 100. The differences from the HIGH scoring subgroup are given outside of the parentheses; the differences from the LOW scoring subgroup are given inside the parentheses. Differences between normal controls and all patients with schizophrenia can be obtained by a weighted average of the two. Statistical significance (2-tailed t-test) for the HIGH or LOW scoring subgroup comparisons to the normal group are represented by +, $p = 0.06$; *, $p = 0.05$; **, $p = 0.01$. Significance for all schizophrenic patients compared to normal controls is represented by _____, $p = 0.05$ and ═══, $p = 0.001$. These values are uncorrected for the number of comparisons.

regional differences that were contained within larger anatomic areas of the brain that were also found to yield significant group differences on the basis of multivariate analysis. For this purpose, the 55 regions were grouped into right and left frontal, medial frontal, right and left parietal, right and left temporal cortex and subcortical areas. The ones in which metabolic rates were found to differ significantly between the groups by Hotelling's T2 were the right frontal ($p = 0.01$), left frontal ($p = 0.02$), medial frontal ($p = 0.003$), and the left temporal ($p = 0.02$) cortical areas. Subsequent T2 analysis of the frontal cortex by plane demonstrated these differences to be localized to the middle frontal cortex (Planes C, $p = 0.04$ and D, $p = 0.004$, Fig. 1, Table I.) approximating Brodmann areas 10, 45 and 46. Thus, only the lower glucose metabolic rates found in the middle frontal cortex and the left anterior temporal cortex of the schizophrenic patients are deemed reliable and are depicted in Fig. 2.

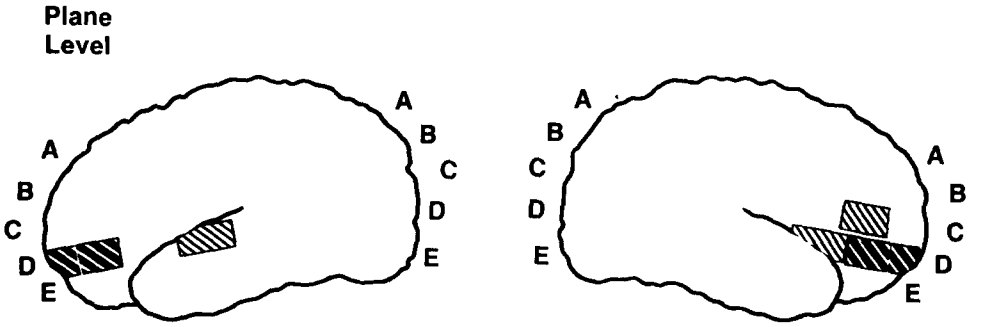

FIG. 2

Schematic representation of statistically significant differences between the regional glucose metabolic rates of the schizophrenic patient group and the normal control group based on standardized data (see Methods and Table I). $p = 0.05$ lower metabolic rates in schizophrenia are represented by the lightly cross-hatched boxes and $p = 0.001$ lower metabolic rates in schizophrenia by the darker cross-hatched boxes.

Examination of the correlations in the normal controls between performance and the glucose metabolic rates of each of the 55 brain regions indicated that only regions in the middle prefrontal cortex had significant inverse associations between metabolic rates and the incorrect identification of distractors (i.e. the higher the rate, the lower the false alarms) (Table II). In contrast, the metabolic rates of patients with schizophrenia, in these same regions, are unrelated to the accuracy of their performance (Table II).

To determine whether the group differences in metabolic rates of the

mid-frontal cortex were due to performance differences, we examined HIGH and LOW scoring schizophrenic patient subgroups (Table I). Those patients with schizophrenia who scored at least as many correct identifications of target tones (hits) as our poorest normal performer (151 hits) were assigned to the HIGH scoring subgroup (mean ± s.d. was 200.7 ± 15.0 hits and 7.57 ± 6.16 false alarms), and those patients who were less effective were placed in the LOW scoring subgroup (89.78 ± 44.15 hits and 44.8 ± 39.8 false alarms). Despite the fact that the mean performance of the HIGH scoring subgroup did not differ from that of the normal control group (191.6 ± 18.2 hits and 5.07 ± 4.7 false alarms), but significantly differed from the LOW scoring subgroup ($p = 0.0001$), both the HIGH and LOW subgroups separately had significantly lower regional glucose metabolic rates in the middle prefrontal cortex than the normal control group, and did not differ from each other in this area (Table I). The only statistically significant regional metabolic difference between the two subgroups was in the left posterior frontal cortex of Plane A where the HIGH scoring subgroup had a higher glucose metabolic rate than both the LOW scoring subgroup ($p = 0.05$) and the normal control group ($p = 0.05$). However, the metabolic rate in this region was not associated with the accuracy of performance in the normal control and schizophrenic groups.

TABLE II
MID-PREFRONTAL CORTEX GLUCOSE METABOLIC RATE--PERFORMANCE ASSOCIATIONS

	Normal Controls	Schizophrenic Patients
Brain Region		
Plane C		
medial	-0.490** (0.375)	0.014 (-0.067)
R anterior	-0.454* (0.264)	-0.123 (0.237)
L anterior	-0.401* (0.333)	-0.259 (0.041)

The significant within group Pearson product-moment correlations observed between regional glucose metabolic rates of the frontal cortex and performance are reported. The numbers outside of parentheses represent correlations to false alarms; a negative correlation indicates that higher metabolic rates in the region of interest are associated with fewer errors. The correlations within parentheses are with hits; a positive correlation indicates that higher glucose metabolic rates in the region of interest are associated with a greater number of hits. Statistically significant associations, uncorrected for number of comparisons, are represented by *, $p = 0.05$ and **, $p = 0.01$.

Discussion

Despite the dramatic differences in the behavior of schizophrenic patients, positron emission tomographic (PET) scans of the brain metabolism of schizophrenic patients closely resemble those of normals. Of those small differences that have been observed in this population compared to normals, the most common finding has been that of "hypofrontality" (18). As noted by Ingvar and Franzen (19) the normal pattern of functional activity in resting man is hyperfrontal. Measures of metabolism and blood flow that reflect brain functional activity show higher activity in the frontal cortex, an area

regarded as important for the performance of the highest integrative or executive functions of the brain, as opposed to other more posterior areas that are more closely associated with the receiving and processing of sensory stimuli. It is the attenuation of this pattern in schizophrenia that has been observed by some investigators (20-23) but not by others (24,25).

Consistent with this hypothesis are the diversity of information processing deficits that have been observed in schizophrenia (26-32) and the broad range of experimental data that implicate the prefrontal cortex in information processing (32-39). However, as the frontal cortex is quite large in man and consists of a number of functionally somewhat independent entities (34,39), it is not surprising that observations of hypofrontality are not restricted to schizophrenia and have depended upon the anatomic regions selected for evaluation and the choice of statistical analysis (18,40). Furthermore, as these studies have frequently demonstrated greater differences in the functional values of the parietal or occipital cortices in schizophrenia than the frontal cortex, the importance of the hypofrontality hypothesis and its implication of disordered "executive" function for understanding schizophrenia remained unclear.

To remedy these problems, we elected to study frontal cortical function in schizophrenia in the context of a specific executive function, maintenance of directed attention. We were able to demonstrate for the first time that regional measurement of glucose metabolic rate in the brain can be directly related to quantitative measures of a normal subject's performance on a cognitive task during the actual period of metabolic measurement. Thus, the observation of midfrontal cortex involvement in the performance of a task requiring sustained attention became the basis from which we could directly examine the functional activity of this region in patients with schizophrenia during the performance of auditory discrimination.

In this context, the lack of associations between metabolic rates in the midfrontal cortex of patients with schizophrenia and the accuracy of their performance on auditory discrimination is the more remarkable because of the greater range and variance of performance observed in the patients with schizophrenia compared to the normal controls in which direct relationships are observed. These data are strengthened by the observations of lower metabolic rates in the midfrontal cortex of both the LOW and HIGH performing subgroups of patients with schizophrenia compared to the normal control group. Together, the findings point to dysfunction of the the middle prefrontal cortex as one basis for the disorder of sustained attention in schizophrenia.

The observation of only a single statistically different regional metabolic rate in the comparison of the LOW and HIGH performing subgroups of patients with schizophrenia could reflect chance, i.e. the small number of patients in each subgroup, the underlying heterogeneity of the clinical syndrome of schizophrenia, or the functional contribution of another brain region to performance differences. Since, the metabolic rate in the cortical region that differed between the two subgroups was not associated with accuracy of performance in either the normal control or schizophrenic groups, the importance of this difference for understanding of sustained attention in schizophrenia or for the role of other brain regions in the performance of auditory discrimination is unclear.

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References

1. H.E. ROSVOLD, A.F. MIRSKY, I. SARASON, E.D. BRANSOME, JR, and L.H. BECK, J. Consult. Clin. Psychol. 20 343-350(1956).
2. A.F. MIRSKY, Ann Rev. Psychology 20 321-348(1969).
3. C. KORNETSKY and M.H. ORZACK, J. Psych. Res. 14 69-79(1978).
4. L.J. SEIDMAN, Psychol. Bull. 94 195-238(1983).
5. K.H. NUECHTERLEIN, J. Abnormal Psychol. 92 4-28(1983).
6. L. ERLENMEYER-KIMLING, Y. MARCUSE, B. CORNBLATT, et al., in CHILDREN AT RISK FOR SCHIZOPHRENIA, N. F. Watt et al. (eds) pp 169-189, Cambridge University Press (1984).
7. J.M. NEALE, K.C. WINTERS, and S. WEINTRAUB, ibid., pp. 264-278.
8. J.C. MAZZIOTTA, and M.E. PHELPS, in POSITRON EMISSION TOMOGRAPHY AND AUTORADIOGRAPHY: PRINCIPLES AND APPLICATIONS FOR THE BRAIN AND HEART, M.E. Phelps, J.C. Mazziotta and H.R. Schelbert (eds.), pp 493-579 Raven Press (1986).
9. M.E. PHELPS, and J.C. MAZZIOTTA, Science 228 799-809(1985).
10. M. REIVICH, and R. GUR, in POSITRON EMISSION TOMOGRAPHY, M. Reivich and A. Alavi (eds.), pp. 329-344 Alan R. Liss (1985).
11. W. GUY, ECDEU: ASSESSMENT MANUAL FOR PSYCHOPHARMACOLOGY, pp. 157-169 publication ADM 76-336 US Dept of Health, Education and Welfare (1976).
12. L. SOKOLOFF, M. REIVICH, and C. KENNEDY, et al., J. Neurochem. 28 897-916(1977).
13. R.A. BROOKS, J. Nucl. Med. 23 538-539(1982).
14. M.E. PHELPS, S.C. HUANG, E.J. HOFFMAN, et al., Ann. Neurol. 6 371-388(1979)
15. C. CLARK, R. CARSON, and R. KESSLER et al., J. Cerebral Blood Flow and Metab. 5 142-150(1985).
16. T. MATSUI and A. HIRANO, AN ATLAS OF THE HUMAN BRAIN FOR COMPUTERIZED TOMOGRAPHY IGAKU SHOIN (1978).
17. E.J. METTER, W.H. RIEGE, D.E. KUHL. and M.E. PHELPS, J. Cereb. Blood Flow and Metab. 4 1-7(1984).
18. R.M. COHEN, W. SEMPLE, AND M. GROSS, Psychiatric Clinics of North America 9 63-79(1986).
19. D.H. INGVAR AND G. FRANZEN, Acta Psych. Scand. 50 425-462(1974).
20. M.S. BUCHSBAUM, D.H. INGVAR, R. KESSLER, et al., Arch. Gen. Psych. 39 251-259(1982).
21. M.S. BUCHSBAUM, L.E. DELISI, H.H. HOLCOMB, et al., Arch. Gen. Psych. 41 1159-1166(1984).
22. T. FARKAS, A.P. WOLF, J. JAEGER, et al., Arch. Gen. Psych. 41 293-300(1984)
23. A. WOLKIN, J. JAEGER, J.D. BRODIE, et al., Am. J. Psych. 142 564-571(1985)
24. G. SHEPPARD, J. GRUZELIER, R. MANCHANDA, et al., Lancet 2 1448-1552(1983).
25. L. WIDEN, M. BERGSTROM, G. BLOMQUIST, et al. in POSITRON EMISSION TOMOGRAPHY OF THE BRAIN, W.D. Heiss and M.E. Phelps (eds) pp. 192-195 Springer-Verlag (1983).
26. D. SHAKOW, Arch. of Gen. Psych. 6 1-17(1962).
27. J. ZUBIN, in EXPERIMENTAL APPROACHES TO PSYCHIATRY, M.L. Kietzman, S. Sutton and J. Zubin (eds) pp. 139-166 Academic Press (1975).
28. P.S. HOLZMAN, D.L. LEVY, and L.R. PROCTOR, Arch. of Gen. Psych. 33 1415-1420(1976).
29. N. GARMEZY, J. Psych. Res. 14 3-34(1978).
30. T.F. OLTMANNS, J. Abnormal Psychol. 87 212-225(1978).
31. R.F. ASARNOW and D.J. MACCRIMMON, J. of Abnormal Psychol. 87 597-608(1978)

32. D.R. WEINBERGER, K.F. BERMAN and R.F. ZEC, Arch. Gen. Psych. 43 114-124 (1986).
33. M-M. MESULAM, Ann. Neurol. 10 309-325(1981).
34. P.S. GOLDMAN-RAKIC, TINS 7 419-424 and 425-429(1984).
35. M. FUSTER, 7 408-418(1984).
36. B. MILNER and M. PETRIDES, TINS 7 403-407(1984).
37. A.F.T. ARNSTEIN, and P.S. GOLDMAN-RAKIC, Ann. N.Y. Acad. Sci. 444 218-234(1985).
38. P.E. ROLAND in BRAIN IMAGING AND BRAIN FUNCTION L. Sokoloff (ed.), pp. 87-104 Raven Press (1985).
39. D.T. STUSS and D.F. BENSON, THE FRONTAL LOBES, Raven Press (1986).
40. R.M. COHEN and T. NORDAHL, in MODERN PERSPECTIVES IN CLINICAL PSYCHIATRY, J.G. Howells (ed) Brunner/Mazel in press.