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Diminished cerebral metabolic response to motor stimulation in schizophrenics: a PET study

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Abstract Positron emission tomography (PET) and the deoxyglucose method were used to measure cerebral metabolism in 14 normals and 13 schizophrenics at rest and during performance of simple and complex finger-movement sequences. The normals, but not the schizophrenics, showed significant metabolic activation in mesial frontal and contralateral sensorimotor and premotor regions during the complex movement. The relative metabolism of schizophrenics was significantly lower than normal in frontal regions and higher than normal in thalamus and basal ganglia under *all* scanning conditions. The results suggest that schizophrenics may have a brain dysfunction which limits their capacity to produce a focal metabolic response to stimulation in several functionally distinct brain regions.

Key words Schizophrenic brain dysfunction · PET in schizophrenia · Motor dysfunction · Cortical activation in schizophrenia

Introduction

Since Kraepelin differentiated Dementia Praecox from affective illnesses there has been speculation concerning the anatomical basis for schizpohrenic disorders (Kraepelin 1971; Bleuler 1950). Much of the initial neuropathological work has been difficult to duplicate and appears to have been done without appropriate control groups (Kirch and Weinberger 1986). In recent years it has been possible to carry out controlled studies using live patients with a variety of techniques including computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET), and regional cerebral blood flow (rCBF). The former two techniques allow quantitative estimates of anatomical structures, whereas PET and rCBF are able to look at aspects of metabolic or neurotransmitter function or blood flow in specified brain regions. The *anatomical* studies point to smaller brains (Bogerts et al. 1985; Brown et al. 1986; Pakkenberg 1987, 1992), larger ventricles (Nasrallah et al. 1986; Takeuchi et al. 1994), and subtle changes in the medial temporal and limbic areas (Schiebel and Kovelman 1981; Jakob and Beckmann 1986; Suddath et al. 1989; Falkai et al. 1988; Bogerts et al. 1990; Colombo et al. 1993; Seidman et al. 1994). These findings are reasonably consistent across methodologies, including postmortem neuropathological examination, CT scans, and MRI studies. A study using monozygotic twins discordant for schizophrenia again found these abnormalities in the ill twin, suggesting that the structural changes may not be genetic in nature (Suddath et al. 1990). The *functional* studies have been somewhat less consistent but suggest that the frontal lobes may be dysfunctional, with metabolic hypofrontality reported in many PET studies but not all (Wolkin et al. 1985, 1992; Buchsbaum et al. 1984, 1986, 1990, 1992; Weinberger and Berman 1988; Siegel et al. 1993) and lack of activation, e.g., of the dorsolateral prefrontal cortex found in rCBF studies using the Wisconsin card-sorting task as activation (Weinberger et al. 1986, 1988). However, a central question in the rCBF studies is the specificity of a task probing a hypothesized dysfunctional area; the specificity between Wisconsin card-sorting test performance and frontal dysfunction has been questioned recently, suggesting that other factors are involved also in schizophrenic patients' dysfunction with this challenge (Metz et al. 1994; Seidman et al. 1994).

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We have chosen to examine the question of specificity by looking at the activation of mesial frontal and left sensorimotor regions, because single photon emission CT (SPECT) findings obtained with the Xenon-133 inhalation method suggested dysfunction of primary motor cortical regions (Guenther et al. 1986, 1991). We used for this PET study a paradigm developed by Roland et al. (1980, 1982) that compares activation during a complex finger-sequencing task with activation during a repetitive finger-movement-control task. We have taken advantage of the stability of the deoxyglucose method in a repeated-measures design (Bartlett et al. 1988) to assess metabolic activity during performance of the two tasks in schizophrenics and normal controls. Both medicated and unmedicated schizophrenic patients were used, and metabolic activation in multiple cortical and subcortical brain regions was examined.

Patients and methods

Schizophrenics

A group of 13 right-handed male inpatients in a stable phase after an acute exacerbation of the disease (age range 20–43 years; mean age 30.5 years; SD 6.8 years) participated in the study. All patients were interviewed independently by two participating psychiatrists and fulfilled DSM-III-R and RDC criteria for chronic schizophrenia. No patient with a history of drug or alcohol abuse, brain injury, or abnormal neurological or metabolic history was included in the study. Patient characteristics are summarized in Table 1. Nine patients were studied on a maintenance neuroleptic treatment protocol. Individual plasma haloperidol concentrations ranged between 5.3 and 21.8 ng/cc on the morning of the PET investigations. Four subjects were studied while neuroleptic-free. Of these, 1 was medication-naive and the others were medication-free for at least 1 year (range 1–5 years). No differences in psychopathology or stability of symptoms were observed between drug-free and neuroleptically treated patients.

Normal controls

A total of 14 right-handed male persons volunteered for the study after an advertisement action in the geographical area of New York University (age range 21–41 years; mean age 26.0 years; SD 5.4 years). Upon medical examination all were found to be clinically healthy with no history of drug or alcohol abuse and no abnormal neurological, metabolic, or psychiatric history. Handedness in all subjects was determined by the Edinburgh Handedness Questionnaire (Oldfield 1971). The study had the approval of the participating institutional review boards and their respective radiation safety committees. All subjects were paid a constant free according to our institutional volunteer subject guidelines and gave informed consent to participate. No payment deduction was considered for performance quality.

PET scan procedures

All subjects were scanned in the low-resolution mode on the PETT VI at Brookhaven National Laboratory (spatial resolution at full width of half-maximum = 11.8 mm in the plane of section and 14.4 mm in the axial direction). Prior to the first isotope injection each subject's head was positioned in a plane parallel to the canthomeatal line. Transmission scans were then performed using a $^{68}Ge/^{68}Ga$ ring source. These were used for attenuation correction and to define the size and center of the brain for each PET image. Catheters were inserted into a dorsal vein of the left hand for blood sampling and a right antecubital vein for isotope administration 45 min before the first injection. Each subject's left hand was heated to maintain skin temperature at 44° C in order to arterialize venous blood (Phelps et al. 1979).

Plasma from arterialized blood was assayed for radioactivity after each injection. No control for oxygen tension was performed. Each subject received three isotope injections of a bolus of between 5.8 and 6.5 mCi of ^{11}C-2-deoxyglucose (CDG) each (MacGregor et al. 1978), administered at approximately 10:30 a.m., 12:30 p.m., and 2:30 p.m. on a single day. No corrections for remaining radioactivity between investigations were necessary given the 22-min half-life of 11-CDG. Scans were obtained at 35 min and again at 45 min after injection. Seven simultaneous images were obtained from each scan. After the 35-min scan the subject was moved 7.2 mm, which resulted in a set of 14 interleaved PET images slightly displaced in time.

Table 1 Patient characteristics

Patient no.	Age (years)	Education (years)	Diagnosis	Duration of illness (years)	Medication status[a]	BPRS[b]	AIMS[c]	Error[d]
1	33	12	Undifferentiated	20	Off	42	0	–
2	20	14	Paranoid	2	Off	34	0	Low
3	24	11	Undifferentiated	3	Off	26	0	High
4	32	12	Paranoid	10	On	32	12	Low
5	36	11	Paranoid	15	On	22	0	Low
6	32	5	Undifferentiated	20	On	30	8	High
7	28	9	Undifferentiated	9	On	24	6	High
8	22	10	Paranoid	5	Off	37	0	Low
9	43	6	Disorganized	20	On	32	1	High
10	35	7	Undifferentiated	15	On	26	14	High
11	27	11	Undifferentiated	11	On	30	0	Low
12	35	12	Paranoid	9	On	26	0	–
13	33	13	Disorganized	14	On	36	18	Low

[a] On or off haloperidol treatment regimen (see text)
[b] Score on day before PET scan (Overall and Gorham 1998)
[c] Score on day before PET scan (Guy 1976)
[d] Number of errors produced on finger-sequencing task (see text; data for patients 1 and 12 are missing)

Experimental conditions

Baseline

The subjects lay quietly on the scanner table with eyes open and ears unoccluded. They were instructed to relax, refrain from conversation, and remain awake.

Repetitive motor task

The subjects flexed their right thumb against their index finger repeatedly at the rate of approximately once every 1.5 s.

Complex motor-sequence task

This is similar to the motor-sequence task of Roland et al. (1980). The subjects produced a sequence of finger movements in which the thumb of the dominant (right) hand is flexed against the fingers as follows: thumb against the index finger twice, against the middle finger once, against the fourth finger three times, and against the little finger twice. The sequence is then reversed.

All subjects were scanned first in the baseline condition. Seven normal and six schizophrenic subjects performed the repetitive and then the sequencing task. Seven normal and seven schizophrenic subjects were studied in the reverse order. All motor tasks were performed for the first 15 min after injection. The subjects then lay quietly until they were positioned for scanning. The tasks were performed with eyes open and ears unoccluded, and were videotaped for later analysis of errors and rate of movement. The subjects were pretrained on each task. In addition to videotaping motor performance as a control for vigilance, in 9 of 13 schizophrenic subjects vigilance was reassured by simultaneous EEG recordings (yielding also PET/EEG "coupling" information; Guenther et al. 1993).

Baseline control subjects

Additional data were obtained from the PET scans of 11 healthy right-handed male volunteers (mean age 21.2 years; SD 1.9 years) scanned twice in a baseline resting condition with eyes open and ears unoccluded under a protocol described by Bartlett et al. (1988). Each subject received two injections of CDG in a single day. The metabolic images of these subjects were reanalyzed for the present study according to the procedures described herein.

Image analysis

Regions of interest (ROIs) were obtained from nine contiguous images located between approximately 10.3 and 4.7 cm above the canthomeatal line. Scan sections were not standardized among subjects. MRI or CT images from approximately the same planes of section were available for 9 normal and 10 schizophrenic subjects who performed the motor tasks, and 7 of the baseline control subjects. For these subjects ROIs were first outlined on the MRI or CT images and then transferred by computer software onto corresponding metabolic images. For all other subjects regions were outlined by drawing boundaries from the standard neuroanatomical atlas of Matsui and Hirano (1978) onto corresponding PET images. Comparisons of ROI values obtained by the CT/MRI method vs the Matsui/Hirano method showed no significant differences between methods for any ROI (Bartlett et al. 1994).

Metabolic values were obtained from 18 ROIs chosen on the basis of physiology and the spatial resolution of the camera (Fig. 1). These included four frontal regions hypothesized to subserve *motor activation*: a bilateral mesial area anterior to the central sulcus (MF), a contralateral (left) sensorimotor area (LSM) adjacent to the central sulcus and contralateral premotor (LPM) and prefrontal (LPF) regions; three *control motor homologue* regions: ipsilateral (right) sensorimotor (RSM), premotor (RPM), and pre-

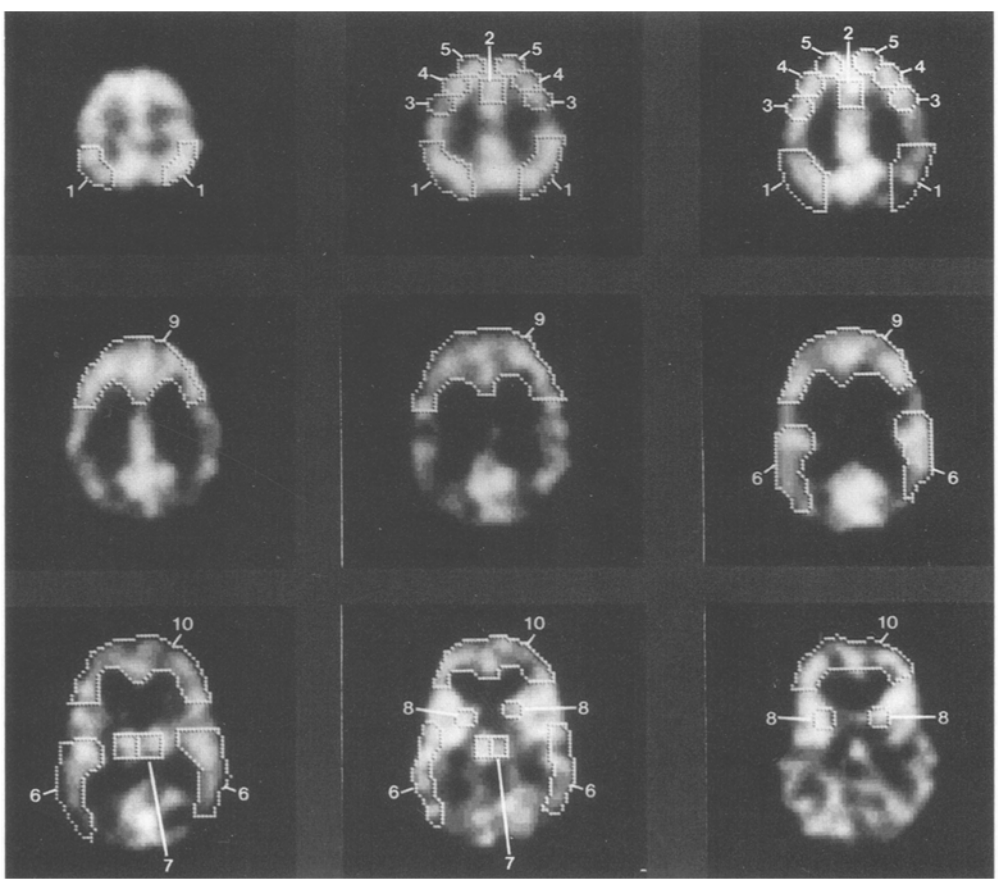

Fig. 1 Regions of interest (ROIs) obtained from nine contiguous positron emission tomography (PET) images located between approximately 4.7 and 10.3 cm above the cantholeatal line. ROIs were first outlined on a subject's CT or MRI image and then transferred by computer software onto a comparable PET image (see text). The outermost cortical boundaries were drawn by computer software at the outermost pixels representing the 30th percentile of metabolic activity for a given image. This cut-off best approximates the outermost limit of cortical tissue as determined in our laboratory by transmission scans and CT. *1* left, right parietal region; *2* mesial frontal region; *3* left, right sensorimotor region; *4* left, right premotor region; *5* left, right prefrontal region; *6* left, right temporal region; *7* left, right thalamus; *8* left, right basal ganglia; *9* left, right middle frontal region; *10* left, right inferior frontal region

frontal (RPF) regions; four *subcortical regions*: left and right thalamus (LTH and RTH) and basal ganglia (LBG and RBG); and six large *cortical regions* that contained both white and gray matter: two frontal regions implicated in the dysfunction of schizophrenia (Buchsbaum and Haier 1987; Weinberger and Berman 1988), the middle (MdF) and inferior (IF) frontal lobes and the left and right parietal (LP and RP) and temporal (LT and RT) lobes (Fig. 1). Whole-slice values (which included ventricles and gray and white matter) were also obtained for each of the nine contiguous images and a *whole brain region* (WB) was then obtained as the sum of the nine whole-slice regions.

Regions drawn on images obtained from one injection were copied by computer software onto comparable images from the other injections to insure that all regions were of comparable size and shape across all scans for a given subject. The order in which a subject's images were processed was randomly determined to control for the effects of drawing vs copying.

Data quantitation

Reginal cerebral metabolic rates for glucose are reported as the mean metabolic value calculated from the data in the constituent pixels of a given ROIs using the Sokoloff et al. (1977) model as extended by Huang et al. (1980) and modified for the use of CDG by Reivich et al. (1982).

Statistical analysis

to minimize Type-I error multivariate analyses of variance (MANOVAs) were used to make group comparisons across multiple regions. SYSTAT multivariate general linear hypothesis routines were used (Wilkinson 1988). On the basis of our research hypotheses we combined separate regions into five multivariate vectors: (1) a set of frontal regions hypothesized to subserve motor activity (MF, LSM, LPM, and LPF), (2) a set of control motor homologues (RSM, RPM, and RPF), (3) a set of subcortical regions (LTH, RTH, LBG, and RBG), (4) a set of frontal regions (MdF and IF), and (5) a set of temporal and parietal regions (LP, RP, LT, and RT).

Statistical analyses were performed on measures of *regional activation*, which provided information concerning metabolic changes from baseline due to motor stimulation, and measures of *relative metabolism*, which provided information concerning the pattern of regional activity observed within a given scanning condition. Regional activation can be seen as consisting of two components: (1) a change due to the effects of a specific task or probe and (2) a fluctuation due to nonspecific aspects of the scanning experience (e.g., scan order, time of day, and random errors of the method). To control for nonspecific fluctuation we multiplied the metabolic values obtained during the motor tasks by a correction factor that scales each value to the whole brain value obtained during the baseline scan. For each subject the correction factor for the second set of scans was whole brain-1/whole brain-2, and for the third it was whole brain-1/whole brain-3 (Bartlett et al. 1988). Regional activation was then defined as the difference between a scaled motor task regional value and a baseline regional value.

Relative metabolism can be defined as the proportion of total activity contributed by each region and expressed as the ratio region/whole brain. Relative regional rates were computed separately for each subject in each region under each stimulation condition.

Task compliance

Task compliance was measured in two ways: *Response frequency*, defined as the number of finger-to-thumb movements observed during the first and last 4 min of motor activity, was computed for each motor-stimulation condition. *Response error*, defined as the number of erroneous (i.e., out of sequence) finger-to-thumb movements observed during the first and last 4 min of activity, was computed for the finger-sequencing condition.

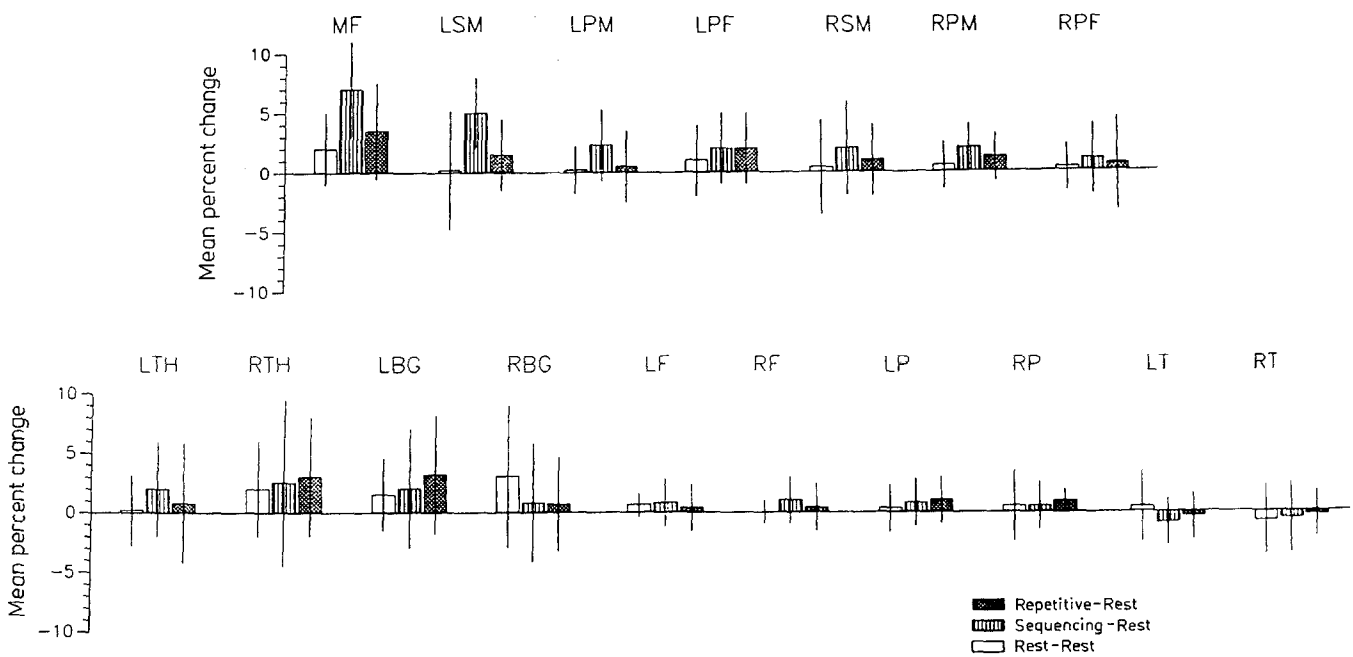

Fig. 2 Average percent change in metabolic activity from baseline to motor stimulation in the group of normal subjects (n = 14) and average percent change from a first to a second baseline scan in the group of baseline control subjects (n = 11). Repetitive-rest is percent change during repetitive movement; sequencing-rest is percent change during finger sequencing; rest-rest percent change from first to second baseline scan. MF mesial frontal; LSM left sensorimotor; LPM left premotor; LPF left prefrontal; RSM right sensorimotor; RPM right premotor; RPF right prefrontal; LTH left thalamus; RTH right thalamus; LBG left basal ganglia; RBG right basal ganglia; LF left frontal;RF right frontal; LP left parietal; RP right parietal; LT left temporal; RT right temporal

Table 2 Results of multivariate analysis of variance (MANOVAs) to test group differences in regional cerebral metabolic activation: normal motor subjects (n = 14) vs normal baseline subjects (n = 11)

		Multivariate results					
Source of variance		Motor		Baseline		F	P
		Mean	SD	Mean	SD		
Rest-sequencing vs rest-rest							
Motor regions (MF, LPF, LPM, LSM)		4	2	1	2	4.71	0.005*
Control motor homologues (RPF, RPM, RSM)		2	2	0.2	2	1.09	0.37
Frontal lobes (MdF, IF)		0.3	2	0.1	1	0.02	0.89
Temporal/parietal lobes (LT, RT, LP, RP)		0.1	1	1	4	0.10	0.75
Subcortical regions (LTH, RTH, LBG, RBG)		2	4	2	2	0.73	0.58
Rest-repetitive task vs rest-rest							
Motor regions (MF, LPF, LPM, LSM)		2	2	1	2	0.28	0.89
Control motor homologues (RPF, RPM, RSM)		1	2	0.2	2	0.41	0.75
Frontal lobes (MdF, IF)		0.3	2	1	1	0.39	0.54
Temporal/parietal lobes (LT, RT, LP, RP)		0.3	1	0.2	2	0.74	0.40
Subcortical regions (LTH, RTH, LBG, RBG)		2	3	2	2	0.08	0.76
		Univariate results					
Source of variance		Motor		Baseline		F	P
		Mean	SD	Mean	SD		
Rest-sequencing vs rest-rest							
Motor regions	MF (RS > RR)	7	4	2	3	7.88	0.01*
	LPF	2	3	1	3	0.14	0.72
	LPM	2	3	0.2	2	3.11	0.09
	LSM (RS > RR)	5	3	0.2	5	9.92	0.004*

* Significant at the Bonferroni-adjusted level of 0.05/4 (P = 0.0125)
Note: Results expressed as percent change: rest-scaled sequencing/rest × 100; rest-scaled repetitive task/rest × 100; rest 1-scaled rest 2/rest 1 × 100. *RS* rest sequencing; *RR* rest-rest (see text for other abbreviations)

Results

Adequacy of task: normal subjects

Figure 2 shows the average regional change in metabolic activity from baseline to motor stimulation in the group of normal subjects as well as the average regional change from a first to a second baseline scan in the group of baseline control subjects.

As can be seen in Table 2 the two groups differed only in the activation of mesial frontal and left sensorimotor areas during motor sequencing. Activation during motor sequencing was found to be focal, restricted only to these regions. The repetitive control task did not result in any significant regional metabolic activation.

Schizophrenic response to motor stimulation

When schizophrenics were compared with normals the only differences were in the motor areas identified previously. As seen in Table 3 the schizophrenics showed a lack of metabolic activation in the mesial frontal and left sensorimotor areas. Figure 3 shows that this was equally true for the medicated and nonmedicated patients. This indicates that regions far from the dorsolateral prefrontal area implicated by the Wisconsin card-sort procedure also fail to activate in response to a complex stimulation task.

Motor-sequencing-task compliance

The rate and accuracy of task performance was assessed for 11 normals and 11 schizophrenic patients from videotapes of the experiment. The groups showed a similar rate, but differed in the accuracy of their performance. The schizophrenics made significantly more errors (Table 4).

To examine the effect of error rate on cortical activation the schizophrenics were divided into groups of high- and low-error subjects (high-error schizophrenics: n = 5; mean error 154 ± 95; low-error schizophrenics: n = 6; mean error 17 ± 15). Each schizophrenic group showed a clear difference from normals in the activation of motor regions (low-error schizophrenics vs normals: F[1, 18] = 6.05; P = 0.02; high-error schizophrenics vs normals: F[1, 17] = 11.86; P = 0.003), but not in the set of control motor homologues (low-error schizophrenics vs normals: F[1,

Table 3 Results of MANOVAs to test group differences in regional cerebral activation: normals (n = 14) vs schizophrenics (n = 13)

Source of variance		Multivariate results					
		Normals[1]		Schizophrenics[1]		F	P
		Mean	SD	Mean	SD		
Rest-sequencing							
Motor regions (MF, LPF, LPM, LSM)		4	2	2	2	8.49	0.007*
Control motor homologues (RPF, RPM, RSM)		2	2	1	3	0.40	0.53
Frontal lobes (MdF, IF)		1	2	0.2	2	1.23	0.28
Temporal/parietal lobes (LT, RT, LP, RP)		0.1	1	1	2	0.53	0.47
Subcortical regions (LTH, RTH, LBG, RBG)		2	4	4	7	0.76	0.39
Rest-repetitive task vs rest-rest							
Motor regions (MF, LPF, LPM, LSM)		2	2	1	2	0.30	0.59
Control motor homologues (RPF, RPM, RSM)		1	2	0.2	2	0.94	0.34
Frontal lobes (MdF, IF)		0.3	2	0.2	2	0.02	0.88
Temporoparietal (LT, RT, LP, RP)		0.3	1	1	2	3.48	0.07
Subcortical regions (LTH, RTH, LBG, RBG)		2	3	2	7	0.001	0.98
		Univariate results					
Source of variance		Motor		Baseline		F	P
		Mean	SD	Mean	SD		
Rest-sequencing							
Motor regions	MF (N > S)	7	4	2	4	9.26	0.005*
	LPF (N = S)	2	3	1	4	0.26	0.61
	LPM (N > S)	2	3	2	4	0.14	0.72
	LSM (N > S)	5	3	2	3	6.60	0.017

* Significant at the Bonferroni-adjusted level of 0.05/4 (P = 0.0125)
Note: Results expressed as percent change: scaled sequencing-rest/rest × 100; scaled repetitive movement-rest/rest × 100
[1] Mean percent change and SD calculated for each set of regions

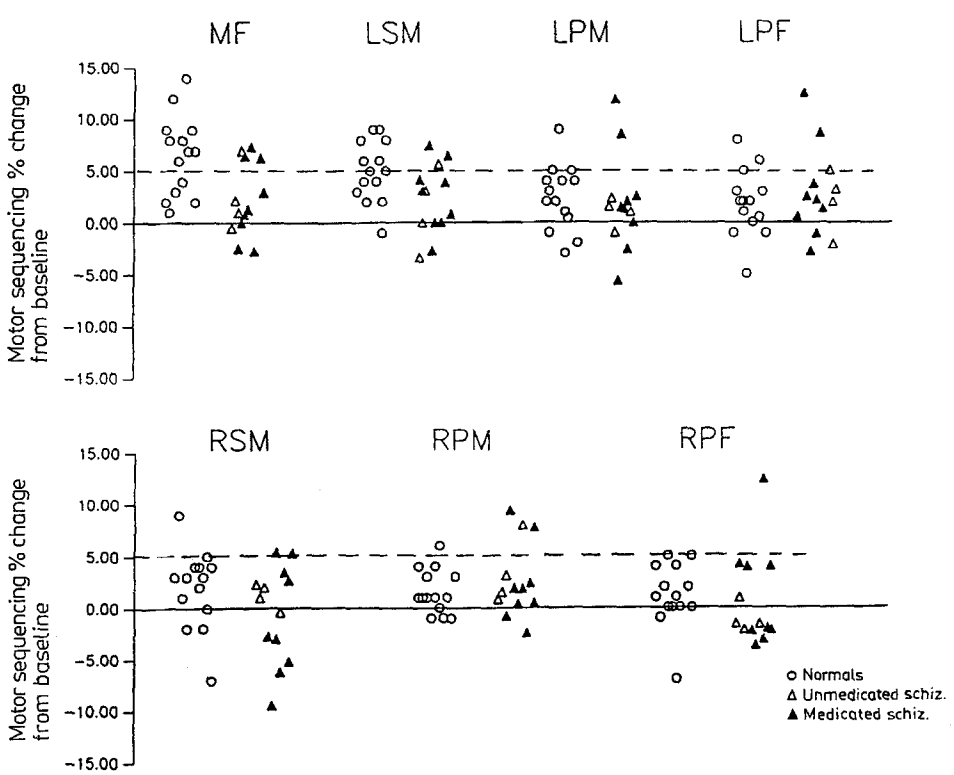

Fig. 3 Percent change in metabolic activity from baseline to motor sequencing in normal (n = 14) and schizophrenic (n = 13) subjects. Normal subjects are represented by *open circles*; medicated schizophrenics by *filled triangels*; unmedicated schizophrenics by *unfilled triangles*. The dashed line indicates a percent change one SD above the percent change observed in the set of motor regions from a first to a second baseline scan (see Fig. 2). MF mesial frontal; LSM left sensorimotor; LPM left premotor; LPF left prefrontal; RSM right sensorimotor; RPM right premotor; RPF right prefrontal

Table 4 Motor-sequencing performance results

	Normals (n = 11)		Schizophrenics (n = 11)		P*
	Mean	SD	Mean	SD	
Number of finger movements					
First 4 min	221.0	51.0	190	60	0.17
Last 4 min	211.0	61.0	201	41	0.85
Number of errors					
First 4 min	1.4	1.5	32	38	0.002**
Last 4 min	2.7	3.2	52	81	0.003**

* All comparisons are by Mann-Whitney U-test
** Significant beyond Bonferroni-adjusted 0.05/4 (P = 0.0125)

Table 5 Results of MANOVAs to test group differences in relative regional metabolism (expressed as the ratio: region/whole brain

Source of variance	Normals[1]		Schizophrenics[1]		Multivariate	
	Mean	SD	Mean	SD	F	P
Motor regions (MF, LPF, LPM, LSM)						
Rest	1.22	0.02	1.21	0.06	0.42	0.52
Repetitive movement	1.24	0.03	1.22	0.06	0.18	0.67
Finger sequencing	1.25	0.03	1.23	0.07	1.71	0.20
Motor homologues (RSM, RPM, RPF)						
Rest	1.19	0.04	1.18	0.04	1.07	0.31
Repetitive movement	1.20	0.04	1.18	0.05	2.24	0.15
Motor sequencing	1.21	0.04	1.18	0.05	1.56	0.22
Frontal cortex (MdF, IF)						
Rest	1.11	0.04	1.07	0.05	5.32	0.03*
Repetitive movement	1.11	0.04	1.06	0.04	9.96	0.004**
Finger sequencing	1.10	0.03	1.06	0.05	7.71	0.01**
Temporal/parietal cortex (LP, RP, LT, RT)						
Rest	1.10	0.03	1.11	0.03	2.61	0.12
Repetitive movement	1.10	0.03	1.11	0.03	0.17	0.69
Finger sequencing	1.10	0.03	1.11	0.03	0.74	0.40
Subcortical regions (LTH, RTH, LBG, RBG)						
Rest	1.19	0.05	1.28	0.11	7.89	0.01**
Repetitive movement	1.21	0.04	1.30	0.08	14.38	0.001**
Finger sequencing	1.21	0.05	1.32	0.08	19.40	0.000**

[1] Mean ratio and SD calculated for each multivariante set of regions
* Trend toward significance
** Significant at 0.01 level or beyond

18] = 1.63; P = 0.22; high-error schizophrenics vs normals: F[1, 17] = 0.00; P = 099). The two schizophrenic groups did not differ from each other in either set of regions (motor regions: F[1, 9] = 1.43; P = 0.26; control motor homologues: F[1, 9] = 0.40; P = 0.53). These data suggest that the failure to activate focal motor areas in response to a complex sequencing task is not "linearly" correlated to the accuracy of task performance in schizophrenics. However, it should be kept in mind that even the "good" schizophrenics performed distinctly poorer (mean error 17) than any normal control (mean error 2).

Relative regional metabolism in normal and schizophrenic subjects

Aside from the activation of specific areas the scans were also analyzed to see if differences in the overall metabolic patterns of schizophrenics and normal controls could be identified under any scanning condition. In all three conditions (rest, repetitive movement, and motor sequencing) the frontal cortex showed less relative metabolic activity and the subcortical regions showed more relative metabolic activity than that found in normals (Table 5). These differences may be related to medication, because they are not seen in the four unmedicated patients. Figure 4 shows the relative metabolic rates in frontal cortex plooted against the relative subcortical metabolic rates of individual subjects during motor sequencing. It is apparent that

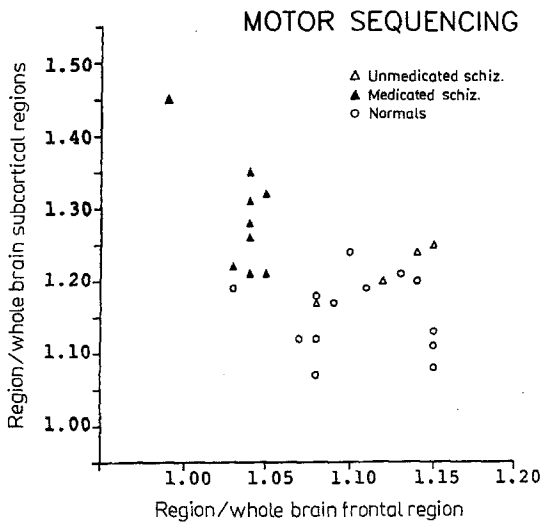

Fig. 4 Frontal and subcortical relative metabolism observed in normal ($n = 14$) and schizophrenic ($n = 11$) subjects during finger sequencing. Relative metabolism is expressed as a ratio of a subject's regional metabolism to his whole brain metabolism: region/whole brain. Subcortical ratios are an average of values calculated from the set of subcortical regions: LTH, RTH, LBG, and RBG. Frontal ratios are an average of values calculated from the set of frontal regions: MdF and IF. Normal subjects are *open circles*; medicated schizophrenics are *closed triangles*; unmedicated schizophrenics are *open triangles*

the metabolic values of the unmedicated schizophrenics are in the normal range.

Discussion

Methodological considerations

Major considerations in any neuroimaging study include the trade-off between sensitivity and reproducibility, temporal and spatial resolution, and the specificity of the response to the putative stimulus. In the present study we used PET and the deoxyglucose method to investigate cerebral metabolism in response to motor stimulation in both schizophrenics and normal subjects. The advantages of this method include its documented intrasubject stability (Bartlett et al. 1988, 1994; Duara et al. 1986) and quantitation (Reivich et al. 1982, 1985). Among the disadvantages are the long time period (approximately 35 min) required for quantitation (Huang et al. 1980) and the possibility that the method is not sufficiently sensitive to metabolic changes induced by the stimulation, because the very stability of the deoxyglucose method creates an insensitivity to mental state (Bartlett et al. 1988).

The motor-sequencing task has been demonstrated to cause a 20%–35% change in rCBF in the supplementary motor (mesial frontal) and contralateral sensory, motor, and premotor areas (Roland et al. 1980, 1982). The use of the deoxyglucose method clearly decreased the sensitivity of these measures, because only a 5–7% metabolic change in these areas was observed. Although the relationship between metabolism, as assessed by the deoxyglucose method, and rCBF is complex, similar patterns of activation are generally found, although the metabolic response is often smaller (Ginsberg et al. 1988; Fox et al. 1988).

The degree of activation may be partly dependent on task duration (Ginsberg et al. 1987). We chose to limit the time of the task to 15 min, which is when subjects began to complain of fatigue and stated that they "go on automatic pilot". This was sufficient to give a detectable metabolic signature while still making it likely that subjects would attend to the task. However, this may have resulted in a diminished measure of activation, because the task was not performed for the entire 35-min isotope-uptake period.

The activation measures were computed on metabolic values, which were scaled to the whole brain metabolic rate. This methodological procedure controls for scan order, time of day, and random-error effects, but does tend to provide a conservative estimate of activation by minimizing the difference between the resting and stimulated measurements. Nonetheless, the resulting activation compares well to the 5% change seen in the rCBF studies using the Wisconsin card-sort (Weinberger et al. 1986, 1988). We failed to detect a metabolic response to the repetitive-movement task in the normal controls. In a topographically organized brain region, such as motor cortex, the number of muscles participating in a task will affect the spatial extent of tissue showing activation. Had we used a task involving a larger number of muscles, we might have obtained a detectable metabolic response.

Normals vs schizophrenics

Response to motor stimulation

In contrast to the focal activation seen in normal controls, the schizophrenic subjects did not activate the mesial frontal and contralateral sensorimotor areas when performing the motor-sequencing task. From our data it appears unlikely that this lack of activation is related to either task accuracy or task speed. Because the sample of unmedicated schizophrenics is small, we cannot determine whether the result is independent of current medication exposure at this time. The contralateral sensorimotor cortex is implicated primarily in the *execution* of voluntary movements (Evarts 1981; Ghez 1985). The function of the mesial frontal (supplementeray) motor area is less certain, but may involve the internal "planning" of movement, either by maintaining the system's "readiness" or "intention" to move (Goldberg 1985) or by specifying the actual subroutines of complex motor sequences (Roland et al. 1980). In any case our results show a failure to activate in two functionally distinct sensorimotor areas.

Weinberger et al. (1986, 1988) have suggested that schizophrenics show a regionally specific inability to activate frontal cortex in response to complex stimuli. They point to their rCBF experiments, which showed an inability to activate prefrontal cortex following the Wisconsin

card-sort task, but no such inability to activate more posterior regions during performance of the Raven's Progressive Matrices. This had led to the suggestion that there is a specific defect in the dorsolateral prefrontal cortex in schizophrenia. Current data suggest that the lack of frontal activation may involve more than this area.

Metabolic patterns

This study also demonstrated a generalized hypofrontal pattern of metabolic activity along with an elevated subcortical metabolic pattern in the brains of medicated schizophrenics. A similar pattern was previously reported in medicated schizophrenics at rest and during visual stimulation (Volkow et al. 1986). However, the significance of these findings remains unclear. Tabulation of data from a large number of normal and schizophrenic subjects has revealed a significant skewing of the schizophrenic sample toward hypofrontality (Buchsbaum et al. 1990; Kishimoto et al. 1987). Nonetheless, hypofrontality is not specific to schizophrenia, because it has been found in patients with affective disorders as well (Buchsbaum et al. 1984, 1986; Baxter et al. 1985, 1989). It is possible that this metabolic pattern may reflect a chronic effect of antipsychotic medication on frontal areas, because 4-week wash-out schizophrenics of similar psychopathology show hypometabolism in frontal *and* basal ganglia areas (Siegel et al. 1993). Furthermore, it has been shown that chronic treatment with antipsychotics can increase relative glucose metabolism in the basal ganglia (Wolkin et al. 1985, 1992; Szechtman et al. 1988; Gur et al. 1987). Because the clinical effectiveness of a neuroleptic seems to be correlated with its potency in binding to dopamine receptors in the basal ganglia (Creese et al. 1984; Schlyer et al. 1992), and because the role of dopamine may be inhibitory in the basal ganglia, it is possible that the increased relative metabolism may be due to the effects of disinhibition and a consequent increase in neuronal activity in the basal ganglia. However, although animal findings suggest that the selective destruction of dopamine efferents in the frontal cortex of rats resulted in increased subcortical dopamine activity (Pycock et al. 1980), is it not yet clear how subcortical hypermetabolism is related to the diminished frontal metabolism observed in normal humans and schizophrenic patients.

Conclusions

This study has demonstrated that schizophrenics show a regionally specific inability to activate metabolically two functionally distinct areas of frontal cortex in response to complex motor stimulation. Other laboratories have reported failures to activate in response to behavioral challenges of various cortical regions. These include: (1) dorsolateral prefrontal cortex in response to the Wisconsin card-sort paradigm (Weinberger et al. 1986), (2) somatosensory cortex in response to pain stimulation (Buchsbaum et al. 1984), (3) frontal and temporoparietal regions in response to the visual Continuous Performance Test paradigm (Buchsbaum et al. 1990) and (4) prefrontal and left temporal regions in response to an auditory discrimination (Cohen et al. 1987, 1988). Taken together these studies indicate that schizophrenics show a failure to activate in several functionally and anatomically distinct frontal regions, and may fail to activate in temporal or parietal regions as well. We propose, therefore, that schizophrenia involves a derangement of brain organization that limits the ability of these patients to produce a focal metabolic response to stimulation of a number of functionally distinct cortical regions, despite their ability to perform the task. This becomes especially obvious in complex demands, which can only be performed with minor quality by these persons.

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