

Abnormal Patterns of Regional Cerebral Blood Flow in Schizophrenia With Primary Negative Symptoms During an Effortful Auditory Recognition Task

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Objective: Using functional brain imaging, the authors sought to replicate their earlier finding of low metabolism in the middle frontal and inferior parietal cortices of schizophrenic patients with primary negative symptoms.

Method: According to the presence or absence of enduring negative symptoms, patients with schizophrenia were classified as having deficit or nondeficit schizophrenia, respectively. Twelve normal volunteers and 18 drug-free schizophrenic volunteers (deficit, N=8; nondeficit, N=10) were trained in a tone discrimination task. They were trained to perform with 70%–80% accuracy and were then scanned with positron emission tomography with [^{15}O]H $_2\text{O}$ during three conditions: rest, sensory-motor control task, and decision task.

Results: Levels of performance of the auditory recognition task were similar in the three groups. An initial hypothesis-driven

analysis revealed that across tasks the deficit group failed to show significant activation in the middle frontal cortex. This was in contrast to both the normal volunteers and nondeficit patients. When the patient groups were contrasted, the deficit patients showed significantly less activation in the middle frontal cortex bilaterally during the control task and in the right middle frontal cortex and inferior parietal cortex during the decision task. An exploratory analysis contrasting deficit and nondeficit patients across conditions did not reveal further differences between groups.

Conclusions: This study replicated the finding of low activation in the middle frontal cortex and inferior parietal cortex in deficit schizophrenia. This deficit was observed without performance confound and may provide a marker of primary negative symptoms and a target for new therapies.

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Schizophrenia is a lifelong psychotic illness that begins in the early adult years. It is characterized by bizarre mental, cognitive, and affective symptoms, of both positive and negative types (1). While some aspects of its biology are known (2), the critical components of its pathophysiology remain to be discovered. Its course includes acute psychotic episodes and quiescent periods with residual symptoms, in highly variable combinations (3–8). Since 1974 it has been recognized that psychosis, negative symptoms, and social functioning are relatively independent domains (9). In 1982 Andreasen and Olson (10) separated positive psychosis into reality distortion and disorganization, and many studies have confirmed the three-factor symptom clusters (1, 11). Whether these symptom dimensions represent distinct illnesses with their own etiologies and pathophysiologies or are merely multiple manifestations of a single illness has been a topic of repeated discussion (9, 12–16).

Primary negative symptoms, often called deficit symptoms, are manifestations of schizophrenia. Studying them to answer questions of etiology and mechanism has often been hampered by the almost ubiquitous confound of sec-

ondary negative symptoms, which influence deficit ratings. Secondary negative symptoms may occur because of depression, paranoia, medication side effects, and other conditions. We have proposed that decisive studies on the biology of deficit symptoms be based on contrasting deficit schizophrenia with nondeficit schizophrenia (14). Already, distinguishing biologic characteristics of patients with primary deficit symptoms have been defined on the basis of genetic (17, 18), risk factor (19), electrophysiologic (20, 21), and biochemical (22, 23) studies. In a preliminary study (24), we showed that patients with deficit schizophrenia had lower levels of neuronal activity at rest in the middle frontal cortex, inferior parietal cortex, and thalamus than did patients with nondeficit schizophrenia.

The development of modern techniques for human brain imaging has powerfully advanced not only our understanding of normal brain function, but also our concepts of human brain diseases. Brains of individuals with a defined CNS illness or subtype can be directly studied in vivo for CNS structural, neurochemical, or functional abnormalities characteristic of the brain disease. Functional human brain imaging is ideally suited to studying sub-

group characteristics in schizophrenia, because the usual illness confounds among the patient volunteers are similar in the subgroups. These confounds include long-term administration of antipsychotic and anticholinergic medication, environmental deprivation, lifelong exposure to trauma and institutionalization, and other factors. Already, imaging techniques have advanced our basic knowledge of schizophrenia (25–35). In particular, several studies have already shown that positive and negative symptom dimensions are associated with different patterns of regional activation. Regional analyses of the correlations between primary negative symptoms and regional cerebral blood flow (rCBF) have implicated the middle frontal regions and inferior frontal cortex (27, 36), as have dichotomies analyses contrasting subjects with and without primary negative symptoms (24, 37).

Therefore, we hypothesized that low rCBF in the middle frontal and inferior parietal cortices bilaterally would occur with performance of an effortful task in deficit schizophrenia. In order to test this hypothesis, we recruited schizophrenic volunteers with and without deficit symptoms but similar in other symptom domains. The two groups were contrasted, without centrally active medication, with matched healthy volunteers free from all CNS disease. Using rCBF measures, we evaluated all volunteers with [^{15}O]H $_2$ O and positron emission tomography (PET), performed during an effortful auditory discrimination task in which performance was matched across groups. We previously reported (38) that when the total group of patients was compared to the normal volunteers, the patients with schizophrenia had less activity in the anterior cingulate.

Method

Volunteers

Eighteen medically healthy schizophrenic persons were recruited from the Residential Research Unit of the Maryland Psychiatric Research Center in Baltimore. Each underwent a Structured Clinical Interview for DSM-III-R (SCID) at hospital admission. Two research psychiatrists (A.C.L., M.A.W.) reached a consensus diagnosis of schizophrenia (according to DSM-III-R criteria) on the basis of the clinical interview and all other sources of data. The diagnosis of deficit syndrome (primary negative symptoms) was made by using the Schedule for the Deficit Syndrome (39). This instrument allows the categorization of schizophrenic patients into those with and those without deficit symptoms on the basis of a semistructured interview. Diagnostic categorization is achieved through the use of operational criteria taking into account six negative symptoms (restricted affect, diminished emotional range, poverty of speech, curbing of interests, diminished sense of purpose, and diminished social drive), their stability over time, and whether the symptoms are primary or secondary (for instance, not secondary to factors such as neuroleptic akinesia, paranoid withdrawal, depressive anhedonia, withdrawal during compelling psychotic experience). This instrument has demonstrated good reliability in the schizophrenic population ($\kappa=0.73$).

The total schizophrenia volunteer group included 15 male and three female persons with a mean age of 31.6 years ($SD=7.7$). Seventeen of the 18 schizophrenic volunteers were right-handed.

The schizophrenic volunteers, all inpatients, were treated with a fixed dose (0.3 mg/kg) of haloperidol and no other neurally active medications for at least 4 weeks before the study. A drug-free period followed haloperidol treatment. All other aspects of inpatient treatment were continued. Symptoms of schizophrenia were assessed repeatedly during the haloperidol baseline and during the subsequent drug-free period by using the Brief Psychiatric Rating Scale (BPRS) (40). Symptoms were rated by two trained raters, and a consensus rating was obtained. Clinical monitoring was continuous, and intervention was available when there was a clinical judgment of significant behavioral change requiring treatment.

Twelve healthy volunteers were recruited from the community through newspaper advertising and were screened by telephone for generally good medical health and the lack of major psychiatric illness. If suitable, they were further screened in face-to-face interviews using the Structured Clinical Interview for DSM-III-R—Non-Patient Edition and the Structured Interview for DSM-III-R Personality Disorders (41) to rule out current or past history of axis I or axis II disorders. Family history of schizophrenia in any first-degree relative of the prospective healthy volunteer was ruled out by clinical interview. Six comparison subjects were male, and six were female. All were right-handed, and their mean age was 28.4 years ($SD=4.6$).

Informed Consent

The normal and schizophrenic volunteers were fully informed about the nature of the protocol, and afterward each gave informed consent. Only patients who were competent and clinically judged to be capable of understanding and appreciating the risks involved in this study were selected to participate. The nature of the protocol was presented on several occasions by separate people, including both the principal investigator (A.C.L.) and noninvestigator clinicians. Family members or care givers were involved in the information process when available.

Tasks

The decision condition was a forced-choice auditory discrimination task. The subject was instructed to immediately press a button held in the right hand when he or she recognized a high-frequency reference tone (1500 Hz) and to press the button in his or her left hand with a lower-frequency tone (800–1492 Hz). Equal numbers of high and low tones, each lasting 100 msec, were randomly presented in each stimulus condition; there were 100 trials in each training set and 60 trials in each imaging set. The interval between trials (onset of first tone to onset of subsequent tone) was 2 seconds. Failure to respond was scored as an error. Response time was calculated as the time from the onset of the stimulus to the button press.

During the active control task (sensory-motor task), the subject heard the same sets of tones that were presented during the decision task. However, he or she was instructed to merely press the right- and left-hand buttons alternately after each tone.

During the rest condition, the subject was instructed to lie quietly. Eyes were open, and earphones were in place during all scans.

Training

All subjects began training on the decision task 2–5 weeks before the scan sessions. Training occurred in a quiet, isolated room. The purposes of the training were to eliminate stimulus or task novelty, determine what frequency difference reliably provided 70%–80% accuracy in performance by the subject, and reduce performance variability within and between volunteer groups. Each volunteer participated in three to five sessions, and there were six training blocks per session. The patients began training during the haloperidol treatment phase and continued throughout the medication withdrawal period.

The tones presented during training were systematically modified by decreasing the frequency difference between the reference and test tones, as the subjects became increasingly accurate in recognizing the two types of stimuli. In the first training session the frequency differences between the high and low tones ranged from 700 to 20 Hz. If a subject was unable to perform with at least 80% accuracy at the largest frequency difference (700 Hz) after three attempts at training, the subject was dropped from further study.

PET Imaging

PET scans were obtained by using the General Electric (Milwaukee) 4096+ system, which produces 15 brain image slices at an intrinsic resolution of 6.1 mm in each dimension. The bolus [^{15}O]H $_2$ O method (42) was used without arterial blood sampling. Approximately 62 mCi of [^{15}O]H $_2$ O were administered on each occasion. Ten to twelve minutes elapsed between scans. The relative CBF distribution was measured in each of three conditions—1) rest, 2) sensory-motor control task, and 3) decision task—with four scans per condition (12 scans per subject). The order of the scans was fixed for all subjects: rest, control task, decision task, consecutively repeated four times. In the rest condition the subject was inactive, with eyes open and ears unplugged; tone stimuli and motor activity were absent, but the earphones were in place. The sensory-motor control task consisted of exposure to the same tones presented during the decision task with alternation of right and left button presses in synchrony with the tones. During the decision task the subject was asked to press the right button when a high-frequency tone was recognized and the left button when a low-frequency tone was detected. Within a given scan the frequencies of the two tones were held constant. The frequencies were chosen on the basis of the training accuracy for that individual. Sixty trials were delivered during each scan; the tones began 15 seconds before tracer delivery, and scan acquisition began 20 seconds after dose delivery. PET data were acquired for 60 seconds.

Image Analysis

The quantitative PET blood flow images were analyzed with modified statistical parametric mapping routines (43). The scans from each subject were realigned by using the first one as a reference. The alignment procedure was modified to use 10 iterations to optimize the spatial correlation between data sets; the default procedure uses three iterations. After realignment, all images were transformed into a standard anatomical space (44). Before generation of the statistical parametric map, the data were smoothed by using a 12-mm Gaussian kernel. Only clusters of connected voxels (face or edge) above a threshold ($z=2.33$, $p=0.01$, one-tailed, uncorrected for multiple comparisons) were tested for significance by means of spatial extent statistical theory, and significance was set at an alpha level of <0.05 after correction for multiple comparisons (43). The full width at half maximum of the average noise subtraction image was used to determine the number of resels (45) available for analysis. Task-related changes in rCBF between the control task and rest and between the control task and decision task were evaluated for each volunteer group; increases and decreases were assessed. Patients with deficit schizophrenia were compared to patients with nondeficit schizophrenia on the same contrasts. The spatial/anatomical distribution and extent of each cluster was mapped onto matching magnetic resonance images aligned and warped to “fit” the statistical data. For hypothesized effects, an uncorrected significance level of $\alpha=0.05$ was used to determine significant areas of activation. For all other analyses, a multiple comparison correction was used. In regions of hypothesized differences, the maxima of significant clusters in the statistical parametric mapping analysis

were grown to a $3\times3\times3$ -pixel sample volume; adjusted rCBF values were obtained in these samples for each task condition.

By means of Pearson's product moment correlations, days of medication withdrawal in all patients were correlated with rCBF in regions showing differences between patients with deficit and nondeficit schizophrenia. Similarly, negative symptoms as measured on the BPRS withdrawal subscale were correlated with rCBF in these regions for the patients with deficit schizophrenia only.

Behavioral outcome measures were extracted from all trials generated in the PET scan sessions during the control and decision tasks. These measures include mean accuracy, mean response time, and mean frequency differences between high and low tones for accurate trials. Differences among the three groups on those measures were each tested by using a Kruskal-Wallis test. Significant results were further tested by performing a Wilcoxon rank sum test on all pairs.

Results

Task Performance by Each Group

Of the 18 schizophrenic volunteers in this study, eight met the criteria for deficit schizophrenia while 10 patients did not. The two patient groups, deficit and nondeficit schizophrenia, were similar on several key demographic elements, including age, length of illness, expression of positive symptoms (score on BPRS psychosis subscale), and parental socioeconomic status (Table 1). The patients with deficit schizophrenia had a significantly higher score on the BPRS withdrawal subscale.

The mean duration of antipsychotic medication treatment was 8.3 years ($SD=7.0$) for the deficit group and 5.5 years ($SD=5.9$) for the nondeficit group; the difference was not significant. There were no differences in either smoker status (yes/no: deficit group=5/3, nondeficit group=7/2) or history of drug or alcohol problems (yes/no: deficit group=2/6, nondeficit group=4/5) between the patient groups. Before scanning, the volunteers with deficit schizophrenia had been withdrawn from antipsychotic medication for a mean of 22.6 days ($SD=14.1$), and those with nondeficit schizophrenia had been without medication for 21.9 days ($SD=13.3$).

Training exposure was not significantly different among the three groups of volunteers. The mean number of blocks of tone recognition trials needed to achieve 70%–80% accuracy was 28.3 ($SD=6.1$) for the deficit patient group, 30.6 ($SD=16.0$) for the nondeficit patient group, and 29.4 ($SD=12.0$) for the healthy comparison group.

Response times and levels of accuracy in performance of the auditory recognition task during rCBF imaging were similar in the deficit, nondeficit, and healthy volunteers (Table 2). However, there was a significant difference among the three groups in the frequency difference between the high and low tones (Kruskal-Wallis $\chi^2=12.27$, $df=2$, $p<0.003$). Further analysis of the overall frequency difference revealed a significant difference between the normal and nondeficit groups and between the normal and deficit groups (Table 2) but no difference between the two groups of patients with schizophrenia.

TABLE 1. Characteristics of Schizophrenic Patients With and Without Primary Negative Symptoms (Deficit Schizophrenia) in a Study of Regional Cerebral Blood Flow During an Auditory Recognition Task

Schizophrenia Group	Sex	Race	Age (years)	Length of Illness (years)	Schizophrenia Subtype	Scores on BPRS ^a			Parental Socioeconomic Status ^b	Score on Premorbid Adjustment Scale ^c	Score on Prognostic Scale ^d
						Psychosis ^e	Withdrawal ^f	Total			
Nondeficit											
1	M	Caucasian	21	3	Paranoid	3	7	26	4	0.48	6
2	M	African American	25	8	Paranoid	9	3	45	3	0.03	5
3	M	Caucasian	36	10	Paranoid	3	5	21	1	0.38	2
4	M	Caucasian	25	12	Paranoid	7	7	32	2	0.47	1
5	M	Asian	40	20	Undifferentiated	11	3	35	1	0.70	2
6	M	Caucasian	23	3	Paranoid	10	3	40	4	0.45	2
7	M	Caucasian	23	2	Undifferentiated	3	3	21	3	0.35	8
8	F	Caucasian	38	6	Paranoid	5	4	26	2	0.15	5
9	M	African American	43	10	Paranoid	11	3	33	1	0.13	10
10	M	Asian	38	22	Paranoid	10	10	48	4	0.25	6
Mean			31.2	9.6		7.2	4.8	32.7	2.5	0.34	4.7
SD			8.5	6.9		3.4	2.4	9.5	1.3	0.20	3.0
Deficit											
1	F	Asian	27	8	Paranoid	7	8	34	2	0.20	2
2	F	African American	27	3	Paranoid	3	9	25	2	0.01	1
3	M	Caucasian	39	24	Paranoid	12	5	42	3	0.60	2
4	M	Caucasian	29	4	Paranoid	5	4	24	3	0.24	6
5	M	Caucasian	35	16	Undifferentiated	4	15	54	1	0.31	3
6	M	Caucasian	19	3	Disorganized	3	5	21	3	0.38	2
7	M	Caucasian	32	15	Undifferentiated	8	10	41	3	0.24	3
8	M	Caucasian	39	22	Paranoid	12	7	52	1	0.21	2
Mean			30.9	11.9		6.8	7.9 ^g	36.6	2.3	0.27	2.6
SD			6.8	8.5		3.7	4.8	12.7	0.9	0.17	1.5

^a Obtained the day of the PET scan.^b Determined with the Hollingshead scale.^c Total score on age scales.^d Total score on general items.^e Items 4, 12, and 15.^f Items 3, 13, and 16.^g The patients with deficit schizophrenia had significantly higher withdrawal scores ($t=2.17$, $df=16$, $p=0.05$).**TABLE 2. Performance on an Auditory Recognition Task of Healthy Volunteers and Schizophrenic Patients With and Without Primary Negative Symptoms (Deficit Schizophrenia)**

Group	Percent Accuracy		Reaction Time (msec)		Frequency Difference Between High and Low Tones Providing 70%–80% Accuracy (Hz)	
	Mean	SD	Mean	SD	Mean	SD
Healthy volunteers (N=12)	80.6	4.7	735.0	102.0	17.2	8.3
Patients with nondeficit schizophrenia (N=10)	76.5	9.5	730.3	150.9	245.2 ^a	291.0
Patients with deficit schizophrenia (N=8)	74.5	11.3	860.2	172.3	134.0 ^b	232.1

^a Significantly different from value for healthy volunteers (Kruskal-Wallis $\chi^2=9.02$, $df=1$, $p<0.003$).^b Significantly different from value for healthy volunteers (Kruskal-Wallis $\chi^2=8.15$, $df=1$, $p<0.005$).

Hypothesis-Driven Analyses: Middle Frontal and Inferior Parietal Cortices

The a priori hypotheses that patients with deficit schizophrenia would have low rCBF in the middle frontal and inferior parietal cortices bilaterally allowed an initial hypothesis-testing analysis of the data. Significant clusters on the

statistical parametric mapping analysis (within-group contrasts and between-patients contrasts) that fell within these anatomic areas were analyzed by using a priori criteria.

Within-group contrasts across tasks. All significant task-induced rCBF changes that occurred in the regions hypothesized to show differences are presented in Table 3 for all three groups. For comparison, values are shown for the same regions in groups where no significant effect was seen.

For the normal volunteers, the sensory-motor control task produced no significant activations, relative to the resting condition, in the left or right middle frontal or inferior parietal cortex. The nondeficit patient group showed a significant activation in the right and left middle frontal region. The deficit group showed no significant activations in these cortical regions during this task. No significant decreases during the control task were observed in any group (Table 3).

Compared to the control task, the decision task produced significantly greater activation in the right middle frontal cortex (x , y , z : 34, 38, 12) of the normal volunteer group. Another middle frontal region (x , y , z : 42, 30, 32) was significantly activated in the nondeficit schizophrenia group. However, in the deficit group these regions showed

TABLE 3. Changes in Regional Cerebral Blood Flow (rCBF) in Regions Hypothesized to Show Differences Between Schizophrenic Patients With and Without Primary Negative Symptoms (Deficit Schizophrenia) During an Auditory Recognition Task^a

Contrast and Region						Difference in Normalized rCBF								
						Talairach-Tournoux Coordinates			Healthy Volunteers (N=12)		Patients With Schizophrenia			
											Nondeficit (N=10)		Deficit (N=8)	
Side	Area	x	y	z	Mean	SD	Mean	SD	Mean	SD				
Differences between conditions														
Sensory-motor control task minus rest														
Middle frontal cortex	Right	46	34	44	30	1.5	2.7	3.8 ^b	1.4	0.9	2.1			
	Left	46	−38	34	30	1.3	2.2	3.9 ^b	2.6	−0.4	2.3			
Decision task minus sensory-motor control task														
Middle frontal cortex/inferior frontal cortex	Right	10, 45	34	38	12	3.2 ^b	2.0	1.8	3.0	3.1	4.1			
Middle frontal cortex	Right	9	42	30	32	2.1	2.9	4.0 ^b	2.6	−1.0	3.0			
Differences between nondeficit and deficit groups														
Sensory-motor control task minus rest														
Middle frontal cortex	Left	46	−42	36	32	0.9	2.1	3.4 ^c	2.0	−1.3 ^c	2.4			
	Right	46	38	34	14	0.9	2.3	2.3 ^c	1.8	−1.3 ^c	3.2			
Decision task minus sensory-motor control task														
Middle frontal cortex	Right	9, 46	44	32	36	1.3	2.9	3.6 ^c	2.5	−2.2 ^c	2.6			
		9	38	6	34	1.2	1.2	2.3 ^c	3.1	−1.6 ^c	2.1			
Inferior parietal cortex	Right	40	56	−38	26	−0.1	3.3	2.2 ^c	3.3	−2.2 ^c	3.1			

^a Blood flow was measured under three conditions: rest, an active sensory-motor control task, and an auditory recognition task requiring decisions about tone frequencies. Normalized rCBF values were obtained from a 3×3×3-pixel sample volume centered over the coordinates detailed. Differences between conditions and between groups were determined by statistical parametric mapping analyses. The values for the healthy volunteers are provided for comparison.

^b Significant difference between conditions.

^c Significant difference between nondeficit and deficit groups.

no significant activation. No significant reductions were seen (Table 3).

Deficit versus nondeficit patients. During performance of the sensory-motor control task, the nondeficit patient group showed greater rCBF activation, relative to the resting condition, in the left and right middle frontal cortex than did the deficit group. Table 3 displays the values for the normal volunteers at the same region for comparison.

During the decision task, the patients with nondeficit schizophrenia showed significantly more activation, relative to the control task, in two right middle frontal clusters and one inferior parietal region than did the patients in the deficit group (Table 3).

There was no significant correlation between rCBF activation in these three regions and negative symptoms (measured on the BPRS withdrawal scale) in the deficit group.

Individual rCBF changes in the right middle frontal area (x, y, z: 44, 32, 36) for patients in the three groups during the decision task, relative to the control task, are contrasted in Figure 1. These individual values show that whereas nine of the 10 nondeficit patients demonstrated activation in the middle frontal cortex, seven of the eight deficit patients showed reductions in rCBF.

Exploratory Analysis: Group rCBF Patterns Across Tasks

The usual statistical parametric mapping analysis using hierarchical task subtraction was carried out for each of the three groups. Clusters representing common task-as-

sociated CNS regions were identified without a priori hypotheses.

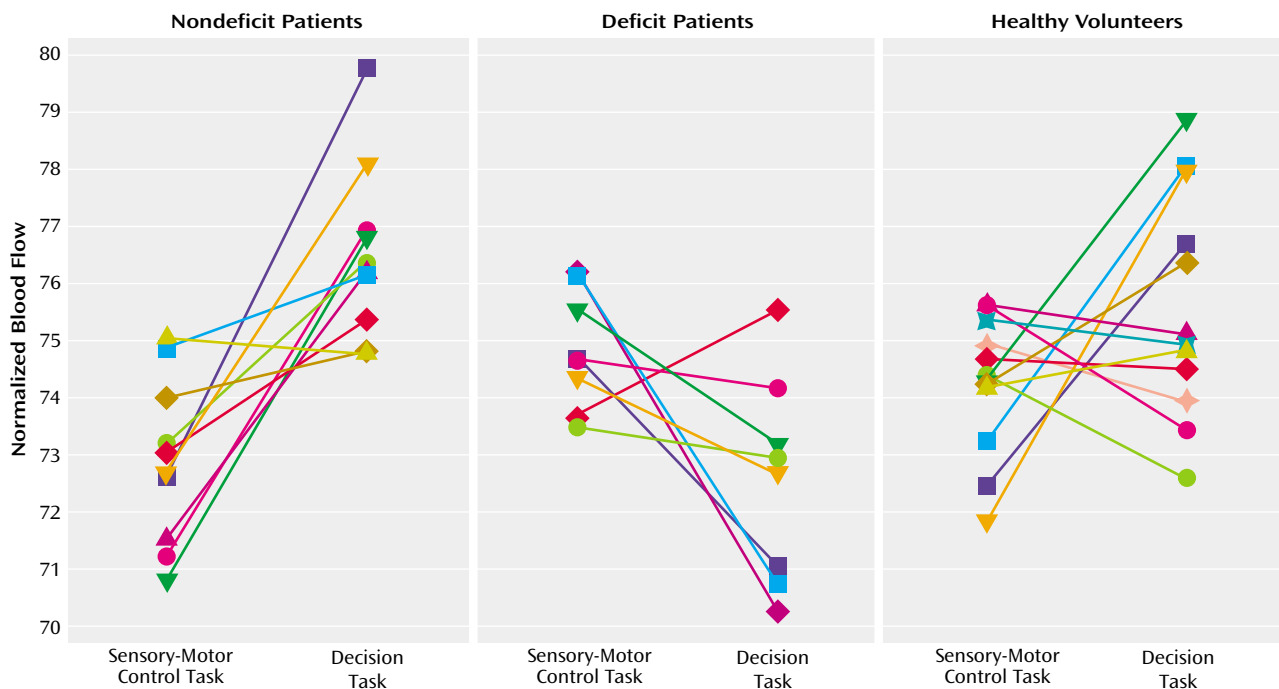
Normal volunteers. The normal rCBF contrast patterns of the healthy volunteers during the control and decision tasks are presented in detail elsewhere (46) and summarized in Table 4. Compared to the resting condition, during the active control condition the auditory cortex of the normal group was activated prominently and bilaterally, along with the inferior frontal cortex bilaterally, the left motor cortex, and the cerebellum. The precuneus, medial frontal cortex, and the posterior middle temporal cortex demonstrated reduced rCBF during the active control condition (Table 4, Figure 2).

The decision condition was associated with significant rCBF activations, compared to the control task, in the right middle and right inferior frontal cortices, the anterior cingulate, the insula, and the cerebellum. The left posterior middle temporal cortex showed a flow decrement (Table 4, Figure 3).

Patients with nondeficit schizophrenia. Compared to the resting condition, the control task produced activations in the auditory cortex, the premotor cortex, the middle frontal cortex, and the supplementary motor cortex, all bilaterally, in the group with nondeficit schizophrenia (Table 5, Figure 2). rCBF was reduced in the right lingual gyrus and the precuneus cortex bilaterally.

For the patients with nondeficit schizophrenia, activation was significantly greater during the decision task than during the control task in the right middle frontal cortical

FIGURE 1. Normalized Cerebral Blood Flow^a in the Right Middle Frontal Cortex^b During a Sensory-Motor Control Task and a Decision Task Performed by Healthy Volunteers and Schizophrenic Patients With and Without Primary Negative Symptoms (Deficit Schizophrenia)^c



^a Normalized to an arbitrary flow value.

^b Talairach-Tournoux coordinates: x=44, y=32, z=36.

^c Nine of the 10 patients with nondeficit schizophrenia had activation in this region, whereas seven of the eight patients with deficit schizophrenia had a reduction in blood flow.

TABLE 4. Changes in Regional Cerebral Blood Flow (rCBF) in 12 Healthy Volunteers During an Auditory Recognition Task^a

Contrast and Region	Side	Brodman's Area
Sensory-motor control task minus rest		
Increases in rCBF		
Inferior frontal cortex	Left	44
	Right	45, 46
Superior temporal cortex	Left	42
	Right	42
Postcentral cortex	Left	3, 1
Cerebellum	Left	
Decreases in rCBF		
Precuneus	Midline	7, 19
	Left	18
Medial frontal cortex	Midline	8
Middle temporal cortex	Right	21, 37
Decision task minus sensory-motor control task		
Increases in rCBF		
Cingulate and medial frontal cortex	Midline	32, 24, 6
Inferior frontal cortex	Right	45
Middle frontal cortex ^b	Right	10, 45
Insula	Left	
Cerebellum	Left	
Decreases in rCBF		
Middle temporal cortex	Left	21
		21, 37
		39, 19

^a Blood flow was measured under three conditions: rest, an active sensory-motor control task, and an auditory recognition task requiring decisions about tone frequencies. Differences between conditions were determined by statistical parametric mapping analyses.

^b Region of hypothesized difference between schizophrenic patients with and without primary negative symptoms (deficit schizophrenia).

region (Table 5, Figure 3). No regions of rCBF suppression could be demonstrated.

Patients with deficit schizophrenia. During the control task, the right postcentral gyrus of the deficit group was more activated than during rest, but the difference fell short of significance (Table 6, Figure 2). The right superior frontal gyrus showed a significant reduction in rCBF during the task (Table 6).

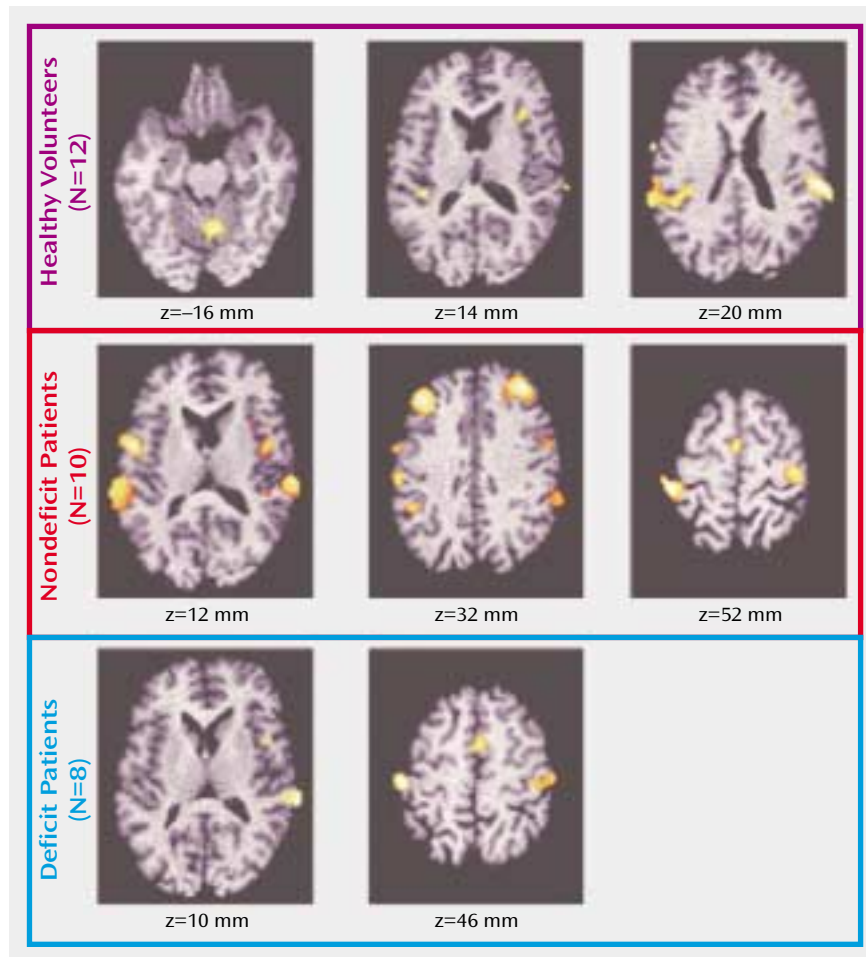
No regions were significantly activated in the decision task, relative to the control task, in the deficit patient group (Figure 3).

Exploratory Analysis: Deficit Versus Nondeficit Patients

Control task contrasted with rest. In the regions hypothesized to show differences between the two schizophrenia groups (Table 3), both the left (x, y, z: -42, 36, 32) and right (x, y, z: 38, 34, 14) middle frontal cortex were significantly more activated during the control task in the patients with nondeficit schizophrenia than in the deficit group (Figure 4, left panel). No other regions showed differences between the patient groups (either increase or decrease).

Decision task contrasted with control task. In the identified regions (Table 3), the patients with nondeficit schizophrenia had significantly more activation than the

FIGURE 2. Changes in Cerebral Blood Flow Between Rest and a Sensory-Motor Control Task in Healthy Volunteers and Schizophrenic Patients With and Without Primary Negative Symptoms (Deficit Schizophrenia)^a



^a In the healthy volunteers, the control task activated limited regions of the cerebellum and the inferior frontal, auditory, and motor cortices, whereas in the patients with nondeficit schizophrenia the control task activated broader and additional regions, including the auditory and motor cortices and the middle frontal and medial frontal cortices. In the deficit schizophrenia group, none of the activations was significant.

deficit group in the right middle frontal cortex (two clusters) ($x, y, z: 44, 32, 36$ and $x, y, z: 38, 6, 34$) and the right inferior parietal cortex ($x, y, z: 56, -38, 26$) (Figure 4, right panel). No other regions showed differences between the patient groups.

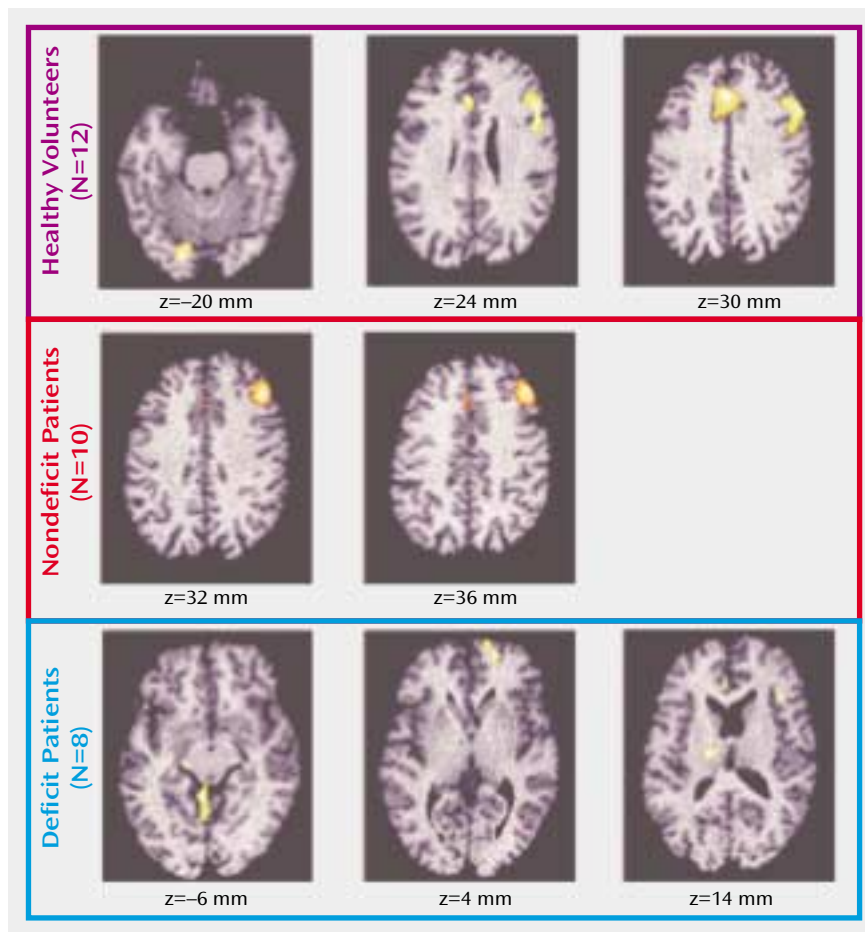
Discussion

These data show that medication-free schizophrenic individuals who differ from each other primarily on the basis of the presence or absence of enduring negative symptoms differ profoundly in the pattern of rCBF abnormalities that is generated with effortful task performance, even when performance of the task is standardized. We have previously reported (46) that the normal individuals scanned for this study experience activation of the auditory and motor cortex with the sensory-motor control condition and activation of the anterior cingulate and right frontal cortex with the effortful decision task. Moreover, the task-activated rCBF pattern of the entire schizo-

phrenia group ($N=18$) differed from the normal pattern only in the anterior cingulate cortex, where rCBF was lower in the patients with schizophrenia (38). Here we report that the deficit schizophrenia group showed low rCBF activation in the left and right middle frontal cortex during the control task and in the right middle frontal and right inferior parietal area during the effortful task. These flow differences occurred despite matched behavioral performance across the three groups. Moreover, these data may explain previous reports of "hypofrontality" in schizophrenia studies with skewed subject subgroups. When the two patient groups in this study were compared to normal volunteers, both showed significant hypoactivation of the anterior cingulate during the effortful task. Neither of the groups showed hypofrontality when contrasted to the normal volunteers.

In this study and in others (9, 12, 14–16, 27), a pathologic dimension within the schizophrenia syndrome was isolated in an attempt to establish homogenous subgroups

FIGURE 3. Changes in Cerebral Blood Flow Between a Sensory-Motor Control Task and a Decision Task in Healthy Volunteers and Schizophrenic Patients With and Without Primary Negative Symptoms (Deficit Schizophrenia)^a



^a During the decision task, the healthy volunteers showed clear activations in the cerebellum, middle and inferior frontal cortices, insula, and anterior cingulate/medial frontal cortex. The patients with nondeficit schizophrenia showed significant activation only in the right middle frontal cortex. The patients in the deficit group did not show significant activation in any brain region, despite task performance.

with distinguishing physiologic, pharmacologic, and anatomic characteristics. Functional imaging analysis provided a critical tool in this comparison of these two populations of psychiatric patients, who were matched on key illness features (positive symptoms and illness characteristics) but were divergent on a single disease characteristic (primary negative symptoms). In this study patients with deficit and nondeficit schizophrenia were prospectively identified by using operational criteria for the presence or the absence of enduring negative symptoms (39). All patients were medication free and trained to perform an auditory discrimination task at similar levels of performance, matched to that of healthy volunteers. Under these conditions, the lower rCBF in deficit schizophrenia in the middle frontal cortex and in the right inferior parietal cortex represents a regional functional deficit without performance confound. Although the patients were medication free for a mean period of 3 weeks, we cannot be certain that their brain function had returned to premedication status at the time of scanning. Postmortem studies

(47) have shown that antipsychotic medications are eliminated slowly from brain tissue. Further preclinical studies (48) reveal slow return of receptor function to normal after exposure to antipsychotic medications. These are important considerations. However, because we did not find any correlations between the number of days of medication withdrawal and rCBF in regions showing group differences, we believe that residual medication effects did not significantly alter the results. The findings presented here replicate and extend the results of our previous PET/fluorodeoxyglucose study (24), in which patients with primary negative symptom had low rates of glucose metabolism at rest in the middle frontal and inferior parietal cortices bilaterally.

These results are limited by several considerations. The number of patients was low, particularly in the group with deficit schizophrenia. So, despite the fact that clusters failed to develop in the deficit group as in the normal subjects, even at nonsignificant levels, low subject number and possibly greater task-associated regional variability

TABLE 5. Changes in Regional Cerebral Blood Flow in 10 Schizophrenic Patients Without Primary Negative Symptoms (Deficit Schizophrenia) During an Auditory Recognition Task^a

Contrast and Region	Side	Brodmann's Area	Talairach-Tournoux Coordinates			Cluster Size	Analysis	
			x	y	z		z ^b	p
Sensory-motor control task minus rest								
Precentral cortex	Left	4, 6	-54	-2	16	2,768	5.14	0.003
	Right	4, 6	40	-16	54		4.27 ^c	0.07
Postcentral cortex	Left	1, 2	-48	-30	52		4.77 ^c	0.009
Superior temporal cortex	Left	22, 42	-62	-40	18		4.55 ^c	0.03
	Right	42	60	-28	18	1,139	4.91	0.03
Middle frontal cortex ^d	Right	46	34	44	30	695	4.61	0.05
	Left	46	-38	34	30	601	4.53	0.054
Supplementary motor area	Midline	6	0	0	52		4.31 ^c	0.06
Rest minus sensory-motor control task								
Precuneus	Right	7	20	-42	52	1,454	4.98	0.004
	Left	7	-20	-70	44	2,593	5.61	0.02
Lingual gyrus	Right	18	20	-58	4	2,065	4.49	0.008
Decision task minus sensory-motor control task								
Middle frontal cortex ^d	Right	9	42	30	32	570	4.95	0.02

^a Blood flow was measured under three conditions: rest, an active sensory-motor control task, and an auditory recognition task requiring decisions about tone frequencies. Differences between conditions were determined by statistical parametric mapping analyses.

^b Score of voxel with maximum value within cluster.

^c Score of individual maximum voxel.

^d Region of hypothesized difference from patients with deficit schizophrenia.

TABLE 6. Changes in Regional Cerebral Blood Flow in Eight Schizophrenic Patients With Primary Negative Symptoms (Deficit Schizophrenia) During an Auditory Recognition Task^a

Contrast and Region	Side	Brodmann's Area	Talairach-Tournoux Coordinates			Cluster Size	Analysis	
			x	y	z		z ^b	p
Sensory-motor control task minus rest								
Postcentral cortex	Right	1, 2	-54	-22	50		4.38 ^c	0.06
Rest minus sensory-motor control task								
Superior frontal cortex	Right	6	30	10	64	103	5.14	0.03

^a Blood flow was measured under three conditions: rest, an active sensory-motor control task, and an auditory recognition task requiring decisions about tone frequencies. Differences between conditions were determined by statistical parametric mapping analyses.

^b Score of voxel with maximum value within cluster.

^c Score of individual maximum voxel.

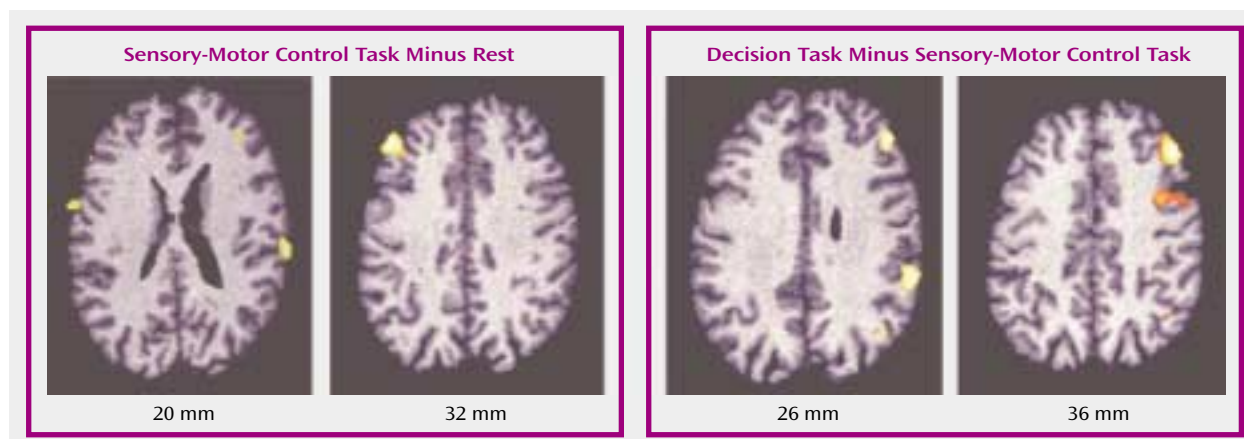
may explain the failure to find an activation in the subjects with deficit schizophrenia. Moreover, although the subject groups were matched on performance, the frequency required to standardize performance at 70%–80% accuracy was highly variable across groups. These limitations introduce added variability into the results. However, these effects appear insufficient to account entirely for these results.

Low frontal cortex metabolism in deficit, but not non-deficit, schizophrenia has been observed in several other functional imaging laboratories (27, 36, 37, 49, 50); low CBF in the inferior parietal cortex has been reported as well (37). These regional associations between brain metabolism and negative symptoms, or the deficit state, in schizophrenia have characteristically been based on correlational analyses (49, 51, 52) or factor analyses (27, 50, 53, 54). Few studies have used a categorical approach (i.e., dichotomization according to a disease characteristic) to contrast flow characteristics across symptom domains (24, 37). Moreover, because antipsychotic medications already reduce regional metabolism in the frontal cortex (55), concurrent treatment with medications becomes a critical confound in studies conducted without withdrawal.

Heterogeneity of cerebral regions that behave abnormally within the diagnostic category of schizophrenia raises the question of whether schizophrenia, as we diagnose it, is a single disease with multiple manifestations or multiple diseases all within a distinct pathophysiology. While these data can illustrate the dilemma, they cannot answer the question. However, these data demonstrate the problem associated with grouping individual results into mean values across all schizophrenia subjects and the possibility of obscuring significant underlying pathology. The dichotomy of primary negative versus nonnegative symptoms of schizophrenia appears to have reduced the heterogeneity in this experiment, and other phenomenologic dichotomies may accomplish the same purpose.

These data provide additional evidence associating human behaviors with lower than normal functioning of the middle frontal cortex and inferior parietal cortex. We can speculate that deficit or primary negative symptoms, like impaired aspects of social affiliation, impaired interpersonal communication, and minimal goal-directed cognitive performance, are generated by functional failures of neuronal populations in these regions. The normal functions of the middle frontal cortex have been inferred from lesion studies and human in vivo functional imaging ex-

FIGURE 4. Brain Regions Activated More in 10 Schizophrenic Patients Without Primary Negative Symptoms Than in Eight Patients With Primary Negative Symptoms (Deficit Schizophrenia) During a Sensory-Motor Control Task and a Decision Task^a



^a As shown in the left panel, the regions significantly more activated in nondeficit than deficit patients during the control task were the right and left middle frontal cortex. Right cluster size: 104 voxels with a maximum z score of 2.61. Left cluster size: 316 voxels with a maximum z score of 3.98. As shown in the right panel, the regions significantly more activated in the nondeficit patients during the decision task were the right middle frontal (two clusters) and inferior parietal cortices. Right frontal cluster sizes: 299 voxels with a maximum z score of 4.81 and 138 voxels with a maximum z score of 3.28. Right inferior parietal cluster size: 185 voxels with a maximum z score of 3.32.

periments. Overall, lesion studies suggest the involvement of this area in personality expression and certain aspects of cognition (56, 57). The specific cognitive processes mediated by the middle frontal cortex depend on region and laterality (58). In vivo functional imaging studies implicate this area (Brodmann's area 9/46) in working memory (verbal on left and nonverbal on right), episodic retrieval, semantic processing, spatial processing (right hemisphere), and attention (59). Multiple type of experiments with humans and primates (60–63) implicate the inferior parietal cortex in visuomotor integration and spatial attention processing. In imaging studies (64–67), the inferior parietal cortex is activated by tasks requiring selective visual attention and spatial processing. Lesions of the inferior parietal cortex in humans are associated with the inability to look on command at a visual target, with optic ataxia, and with oculomotor deficits. Some but not all of the functions associated with these regions are deficient in schizophrenia. Attention, working memory, and executive function are the deficits most often mentioned (68–70). Buchanan and colleagues (11, 71) have reported that subjects with deficit symptoms have worse neurocognitive performance than nondeficit patients. Patients with deficit symptoms may not be able to integrate internal and external representations or sensory cues in an adaptive, rapid manner. Parietal lobe dysfunction may be responsible for this integrative failure. A secondary consequence of parietal lobe failure may be withdrawal from social and environmental novelty.

These data demonstrate functional heterogeneity within the overall diagnosis of schizophrenia, an observation that has implications for diagnosis and clinical management of the illness. This heterogeneity has been reduced by the deficit/nondeficit dichotomization. Whether

both subgroups have the same underlying pathology, only differently distributed, or entirely different pathologies is still a matter of conjecture. In either case, these kinds of data can advance the field by suggesting a focus for studies of postmortem tissue pathology. Prospective analyses of postmortem tissue from these hypothesized regions of the brains of people with schizophrenia have already been productive (72, 73). Although it is premature to suggest the diagnostic use of rCBF patterns, one could propose this rCBF abnormality associated with the deficit state as a surrogate marker of primary negative symptoms in the illness and as a target rCBF pattern for development of new therapies for negative symptoms. Currently there is no treatment for deficit symptoms in schizophrenia, and clinical outcome for this patient group is poor (74, 75). For these reasons, the needs for advances in the treatment of this schizophrenia cohort and technical tools to expedite discovery are particularly pressing.

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