ORIGINAL ARTICLE

Functional Imaging of Memory Retrieval in Deficit vs Nondeficit Schizophrenia

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Background: Neuroimaging studies have provided evidence of abnormal frontal and temporal lobe function in schizophrenia. Frontal cortex abnormalities have been associated with negative symptoms and temporal lobe abnormalities with positive symptoms. The deficit and nondeficit forms of schizophrenia were predicted to differ in prefrontal cortical activity, but not in medial temporal lobe activity.

Methods: Regional cerebral blood flow was studied using oxygen 15 positron emission tomography during 3 different memory retrieval conditions in 8 control subjects, 8 patients with the deficit syndrome, and 8 patients without the deficit syndrome. Behavioral and positron emission tomography data were analyzed using a mixed-effects model to test for population differences.

Results: In all memory conditions, frontal cortex activity was higher in patients without the deficit syndrome than in patients with the deficit syndrome. During the attempt to retrieve poorly encoded words, patients without the deficit syndrome recruited the left frontal cortex to a significantly greater degree than did patients with the deficit syndrome. The 2 schizophrenia subtypes did not differ in the activity or recruitment of the hippocampus during memory retrieval.

Conclusion: Frontal cortex function during memory retrieval is differentially impaired in deficit and nondeficit schizophrenia, whereas hippocampal recruitment deficits are not significantly different between the 2 schizophrenia groups.

Arch Gen Psychiatry. 1999;56:1117-1123

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NEUROIMAGING studies have revealed dysfunctional neural networks in schizophrenia.[1-3] Studies of regional cerebral blood flow (rCBF) and glucose metabolism have found abnormalities in frontal cortex and temporal lobe structures at rest as well as during the performance of cognitive tasks. There is, however, no pattern that is diagnostic for schizophrenia. For example, frontal and temporal cortex activity at rest have been found to be lower by some investigators but not by others.[1] Similarly, frontal cortex recruitment during task performance was found to be decreased in some studies[4-14] but not in others.[15-17]

The clinical heterogeneity of schizophrenia might explain why it is not associated with a pathognomonic abnormality of brain function. For example, frontal cortex activity at rest correlates inversely with the degree of negative symptoms,[18-24] and left medial temporal lobe activity at rest correlates positively with the severity of psychopathology[25,26] or the degree of reality distortion.[23] Similarly, decreased frontal cortex recruitment during the performance of some cognitive tasks occurs primarily in patients with negative symptoms.[4,11]

Negative symptoms such as anhedonia, avolition, and affective blunting may be primary features of schizophrenia or may be secondary to depression or drug treatment. In about 15% of patients with schizophrenia, classified as having *deficit syndrome*, negative symptoms are primary and enduring features.[27] Carpenter and colleagues[28] have postulated that patients with deficit syndrome show more prominent prefrontal cortex deficits than the rest of the schizophrenia spectrum, but that all patients with schizophrenia show medial temporal lobe abnormalities.

Using positron emission tomography (PET), we have recently provided the first evidence for an impaired recruitment of the hippocampus in schizophrenia.[29] Patients with schizophrenia lacked the normal modulation of hippocampal activity associated with different modes of memory recall,[30,31] but frontal cortex acti-

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SUBJECTS AND METHODS

SUBJECTS

We studied 16 male subjects with schizophrenia and 8 male control subjects. Data from 13 patients with schizophrenia and the 8 control subjects were previously analyzed to test for differences between patients with schizophrenia and normal controls.[29]

The patients with schizophrenia were recruited from an outpatient mental health clinic in Boston, Mass, and diagnosed according to *DSM-IV* criteria[33] by an experienced clinician (D.G.). Control subjects were recruited by advertisement. All subjects provided written informed consent. Subjects were excluded if English was a second language or if they had a history of neurological or medical illness, current substance abuse, or lifetime substance dependence. The study was approved by the Human Subjects Committee of the Massachusetts General Hospital and the Central Office Research Review Committee of the Commonwealth of Massachusetts Department of Mental Health.

Eight of the 16 patients with schizophrenia were classified as having *deficit syndrome schizophrenia* and 8 were classified as having *nondeficit syndrome schizophrenia* using the Schedule for the Deficit Syndrome.[32] The patients were assessed by a clinician trained in the administration of the schedule: the total score for negative symptoms ranged from 10 to 15 (minimum, 0; maximum, 24), and the Global Severity Rating scores were 2 (n = 1) or 3 (n = 7).

All subjects were right-handed[34] and the 3 groups were similar in age (controls, 40.0 ± 6.3 years; patients with nondeficit syndrome, 42.6 ± 5.7 years; and patients with deficit syndrome, 40.0 ± 5.0 years). No control subject had a history of a psychiatric disorder as assessed by the Structured Clinical Interview for *DSM-III-R*.[35] The level of education (controls, 14.9 ± 1.1 years; patients with nondeficit syndrome, 12.8 ± 2.6 years; and patients with deficit syndrome, 13.2 ± 1.4 years) was significantly different only between the control and deficit syndrome groups ($P = .02$). The subjects' parental level of education was not significantly different between groups (controls, 12.6 ± 2.7 years; patients with nondeficit syndrome, 11.0 ± 2.6 years; and patients with deficit syndrome, 11.9 ± 0.6 years; controls vs nondeficit syndrome: $P = .24$; controls vs deficit syndrome: $P = .50$; and deficit vs nondeficit syndrome: $P = .33$). Both schizophrenia samples had a similar duration of illness (patients with nondeficit syndrome, 18.1 ± 6.3 years; patients with deficit syndrome, 17.5 ± 7.5 years; $P = .86$).

At the time of the PET experiment, schizophrenia symptoms were assessed with the Positive and Negative Syndrome Scale[36] and Scale for the Assessment of Negative Symptoms.[37] The patients with nondeficit syndrome scored higher on the Positive and Negative Syndrome Scale positive scale (patients with nondeficit syndrome, 17.0 ± 6.3; patients with deficit syndrome, 11.4 ± 2.6; $P = .03$). The patients with deficit syndrome scored higher on the Positive and Negative Syndrome Scale negative scale (patients with nondeficit syndrome, 17.6 ± 3.3; patients with deficit syndrome, 22.6 ± 6.1; $P = .06$) and the Scale for the Assessment of Negative Symptoms (total score: patients with nondeficit syndrome, 32.4 ± 8.1; patients with deficit syndrome, 50.0 ± 15.8; $P = .01$).

All patients with schizophrenia were treated with typical neuroleptic drugs; the 2 schizophrenia groups did not differ significantly in medication dosage (chlorpromazine-equivalent dosages: patients with nondeficit syndrome, 350 ± 216 mg/d; patients with deficit syndrome, 450 ± 195 mg/d; $P = .57$). Two patients with nondeficit syndrome and 5 patients with deficit syndrome were treated with benztropine mesylate (1-2 mg/d).

COGNITIVE TASK

Subjects performed 3 different tasks.[29,30] During the baseline condition, subjects were instructed to complete 3-letter word stems (presented on a computer screen) into the first word that came to mind. Two other conditions (low recall and high recall), followed an off-line study session. During the study session, subjects were presented with a randomized list of 100 target words, consisting of 20 words

vation was not impaired. We report on an extension of our previous sample to a larger group of patients with deficit or nondeficit syndrome[32] similar in sex, age, duration of illness, and medication status. We tested the hypothesis that deficit and nondeficit forms of schizophrenia differ in prefrontal cortical function, but not in medial temporal lobe function. To achieve this goal, we constrained encoding strategies (shallow or deep) to dissociate frontal cortex activation (associated with low recall accuracy) from hippocampal activation (associated with high recall accuracy).

RESULTS

RECALL TASK

The 2 schizophrenia groups did not differ in recall accuracy scores. Recall accuracy was significantly greater during high recall than during low recall in all 3 groups (controls, 0.76 [ie, 76% correctly recalled target words] and 0.28, $P<.001$; patients with nondeficit syndrome, 0.64 and 0.35, $P = .007$; patients with deficit syndrome, 0.62 and 0.34, $P = .001$) (main effect of condition, $F_{1,20} = 255.5$, $P<.001$). The increment in recall accuracy was significantly different between the 3 groups (diagnosis × condition interaction, $F_{2,20} = 8.45$; $P = .006$). This was caused by different recall accuracy for the control group compared with both schizophrenia groups during low recall (patients with nondeficit syndrome vs controls, $P = .01$; patients with deficit syndrome vs controls, $P = .04$) and during high recall (controls vs patients with nondeficit syndrome, $P = .09$; controls vs patients with deficit syndrome, $P = .02$).

PET DATA

First, mean rCBF values were analyzed for each condition (baseline, low recall, and high recall) separately and

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presented once and 20 words presented 4 times. The subjects were instructed to count *T* junctions (ie, perpendicular lines that cross) in each letter of the target words presented once (perceptual encoding strategy) and to count meanings of the target words presented 4 times (semantic encoding strategy). We gave instructions before each study session to count either *T* junctions or the number of meanings of the word presented on the screen. All subjects successfully completed an off-line practice trial to ensure that they were able to follow the instructions. The accuracy of counting the *T* junctions during the study session was not significantly different between the 3 groups ($F_{2,20} = 1.6$; $P = .22$). During scanning, the subjects were asked to complete 3-letter word stems of words presented either once (low-recall condition) or 4 times (high-recall condition). The experiment consisted of 2 runs of each condition. The 2 baseline conditions bracketed the 2 pairs of low-recall/high-recall sessions, which were counterbalanced for order across subjects.

PET SCANNING

The PET facilities and procedures were identical to those previously described.[29,38] Positron emission tomography data were acquired with a General Electric Scanditronix PC4096 15-slice whole-body tomographic scan (General Electric, Milwaukee, Wis). The slice geometry consists of contiguous slices with a center-to-center distance of 6.5 mm (axial field, 97.5 mm) and axial resolution of 6.0 mm full-width half maximum. The axial field of view of the PET camera in a single-bed position precluded total brain coverage. We determined head positioning to ensure maximal coverage of prefrontal areas and complete coverage of the hippocampus. Positron emission tomography images were reconstructed with a conventional convolution-backprojection algorithm, corrected for photon absorption, scatter, and dead-time effects. Subjects underwent six 1-minute scans and inhaled oxygen 15 carbon dioxide beginning 30 seconds after the initiation of the task. Subjects performed tasks while viewing a computer screen and responded verbally. Each scan was followed by a 10-minute washout period.

DATA ANALYSIS

We analyzed the effects of group and condition on recall accuracy with a 2-way mixed factor analysis of variance (subject as random effect) with a grouping factor and with condition as a within-subjects variable. Where indicated by significant effects, we performed post hoc 2-tailed *t* tests.

Realignment of images and transformation into the standard stereotactic space of Talairach were performed as described previously.[39] Images were smoothed with a 2-dimensional gaussian filter with a width of 15-mm full-width at half maximum. Statistical analyses were performed with Statistical Parametric Mapping (SPM) 96 (Wellcome Department of Cognitive Neurology, London, England). Mixed models in SPM 96 require that data be collapsed so that each condition is represented as a single file. That was accomplished with the proportional scaling option in the random-effects kit. The data were then modeled with explanatory variables for group and condition. Main effects and interactions were assessed using *t* statistics subsequently transformed into *z* scores. Considering that a mixed-effects model is appropriate to study population differences and that we had strong localizing hypotheses, we used a threshold for parametric maps of uncorrected $P<.001$ (ie, $z>3.09$). For completeness, and to obviate bias, all activations corresponding to $z>3.09$ are shown. However, this threshold is only appropriate for those territories about which unidirectional a priori hypotheses were posed. Therefore, other loci are shown in italics to reflect their post hoc status. Since our Talairach transformation algorithm is compatible with SPM 95, we used SPM 95 for the creation of the glass brain projections.

The findings of our original study[29] (ie, a lack of hippocampal recruitment but preserved recruitment of prefrontal areas during different modes of memory retrieval in patients with schizophrenia compared with control subjects) were extended to the larger patient sample of this study. Herein, we focus on the comparison between patients with schizophrenia with and without the deficit syndrome. We refer to the control sample only as a reference to illustrate the differences between the 2 schizophrenia subtypes and the normal pattern of memory retrieval.

for all 3 conditions combined, and contrasted between groups to compare rCBF values during memory retrieval (main effect of group). Second, mean rCBF values contrasted between conditions were analyzed across all 3 groups to compare rCBF values during 2 different modes of memory retrieval (main effect of condition). Third, changes in rCBF values during 2 modes of memory retrieval—low-success retrieval (contrast: low recall – baseline) and high-success retrieval (contrast: high recall – low recall)—were contrasted to compare the recruitment of brain areas during memory retrieval between the groups (group×retrieval condition interaction).

MAIN EFFECT OF GROUP

Consistent with our a priori hypothesis, frontal cortex rCBF values (means averaged across all 3 conditions) differed between the 2 schizophrenia subtypes (**Table 1**) (**Figure 1**). Comparable differences were found in the parietal and temporal cortex. When compared with controls, frontal cortex rCBF was markedly reduced in patients with deficit syndrome and much less so in patients with nondeficit syndrome (Figure 1). The most significant difference between patients with deficit and nondeficit syndrome was found in the right prefrontal cortex (Brodmann area 44/9), where the rCBF values for the patients with nondeficit syndrome were mainly in the normal range, whereas all patients with deficit syndrome showed lower rCBF values (**Figure 2**). The same pattern of widespread cortical differences between patients with deficit and nondeficit syndromes was found when each condition (baseline, low recall, and high recall) was tested separately for group effects. Compared with the patients with nondeficit syndrome, the patients with deficit syndrome did not show higher levels of rCBF in any cortical or subcortical region.

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Table 1. Main Effects*

	Region†	x, y, z Coordinates, mm‡	Thresholds§ z	Thresholds§ k
	Main Effect of Group			
Group‖				
Nondeficit > Deficit	R prefrontal (44/9)	44, 14, 32	4.43	188
	L prefrontal (10)	–24, 48, 24	4.15	797
	R parietal (40)	60, –38, 24	4.21	64
	R middle temporal gyrus (21)	58, –50, 8	4.05	47
	R superior temporal gyrus (22/42)	62, –28, 12	3.22	3
Deficit > Nondeficit	None			
	Main Effect of Condition			
Condition				
Low-success retrieval	R prefrontal (11)	6, 56, –12	4.52	207
		18, 22, –12	3.13	3
	R prefrontal (47)	46, 28, 28	3.99	108
		42, 30, –4	3.17	1
	L prefrontal (9)	–22, 34, 36	3.44	15
	R thalamus	2, –20, 4	3.89	33
	R parietal (40)	50, –36, 40	3.14	2
High-success retrieval	*Cerebellum*	6, –56, –4	3.30	5

*R indicates right; L, left.
†The numbers in parentheses refer to Brodmann areas; post hoc findings are in italics.
‡Coordinates refer for the 3 axes (x, y, z) of the Talairach-Tournoux brain atlas.
§The 2 thresholds that define the excursion sets are z = 3.09 and k = 1. The maximum excursion (z) and the vowel extent (k) are reported for each activation.
‖The sample size of each group (deficit, nondeficit, and control) was 8. Subjects are described in the "Subjects" subsection of the "Subjects and Methods" section.

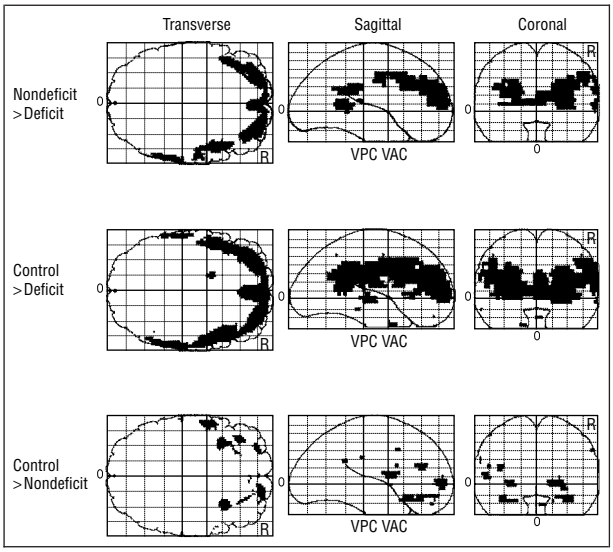

Figure 1. *Statistical parametric maps showing main effects of group on relative regional cerebral blood flow. Significant group differences in regional cerebral blood flow (z = 3.09, k = 1) within orthogonally oriented "glass brains" (created using Statistical Parametric Mapping [SPM] 95) are shown. Note the differential involvement of prefrontal areas in deficit and nondeficit schizophrenia.*

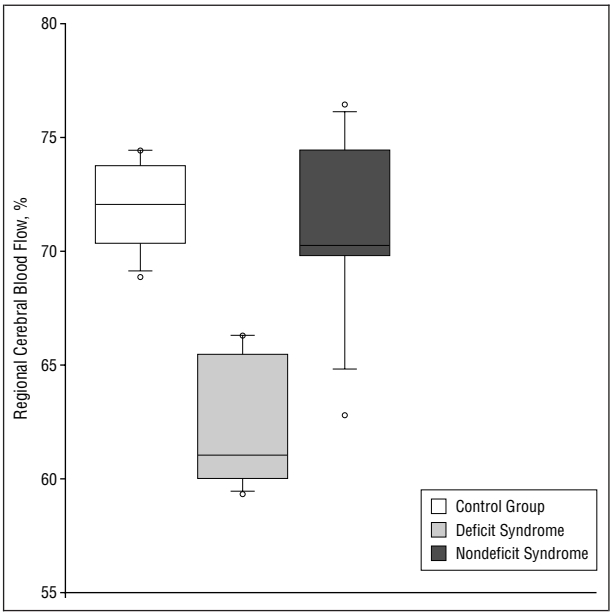

Figure 2. *Box plots of prefrontal cortex regional cerebral blood flow (mean across all 3 conditions for Brodmann area 44/9; coordinates 44, 14, 32) in controls and the 2 schizophrenia subtypes (n = 8 for each group). The 5 horizontal lines in each box represent the 10th, 25th, 50th, 75th, and 90th percentiles; all values above the 90th percentile and below the 10th percentile are plotted separately.*

MAIN EFFECT OF RETRIEVAL CONDITION

In all 3 groups combined, low-success retrieval was associated with the recruitment of the right (areas 11 and 47) and left (area 9) prefrontal cortex as well as the right thalamus and right parietal cortex (area 40) (Table 1). However, during high-success retrieval, the normal pattern of medial temporal lobe recruitment was not found (Table 1).

GROUP × RETRIEVAL CONDITION INTERACTIONS

For the contrast of low recall minus baseline, patients with nondeficit syndrome exhibited significantly greater recruitment of left prefrontal area 47 compared with patients with deficit syndrome (**Table 2**) (**Figure 3**).

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Table 2. Group-by-Condition Interactions*

Group†	Region‡	x, y, z Coordinates§	Thresholds‖ z	Thresholds‖ k
	Low Success Retrieval (Low Recall – Baseline)			
Nondeficit > Deficit	L prefrontal (47)	–34, 30, –8	3.16	6
		–36, 16, –12	3.12	1
Deficit > Nondeficit	None			
	High Success Retrieval (High Recall – Low Recall)			
Nondeficit > Deficit	*R occipital (19)*	40, –78, 16	3.39	4
	R superior temporal gyrus (42)	32, –30, 12	3.34	3
Deficit > Nondeficit	None			

*L indicates left; R, right.
†The sample size of each group (deficit, nondeficit, and control) was 8. Subjects are described in the "Subjects" subsection of the "Subjects and Methods" section.
‡The numbers in parentheses refer to Brodmann areas; post hoc findings are in italics.
§Coordinates refer to the 3 axes (x, y, z) of the Talairach-Tournoux brain atlas.
‖The 2 thresholds that define the excursion sets are z = 3.09 and k = 1. The maximum excursion (z) and the vowel extent (k) are reported for each activation.

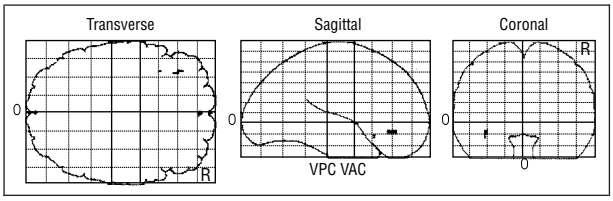

Figure 3. *Statistical parametric maps reflecting the group (nondeficit schizophrenia vs deficit schizophrenia) × condition (low recall – baseline) interaction. Significant differences in regional cerebral blood flow (z = 3.09, k = 1) within orthogonally oriented "glass brains" (created using Statistical Parametric Mapping [SPM] 95) are shown.*

There were no areas of significantly greater recruitment in the patients with deficit syndrome.

For the contrast of high recall minus low recall, there were no significant differences in the frontal or medial temporal lobes between the 2 schizophrenia groups (Table 2). Compared with the control group, both schizophrenia samples failed to recruit the hippocampus ($z = 3.29$ for patients with nondeficit syndrome; $z = 2.99$ for patients with deficit syndrome) (**Figure 4**).

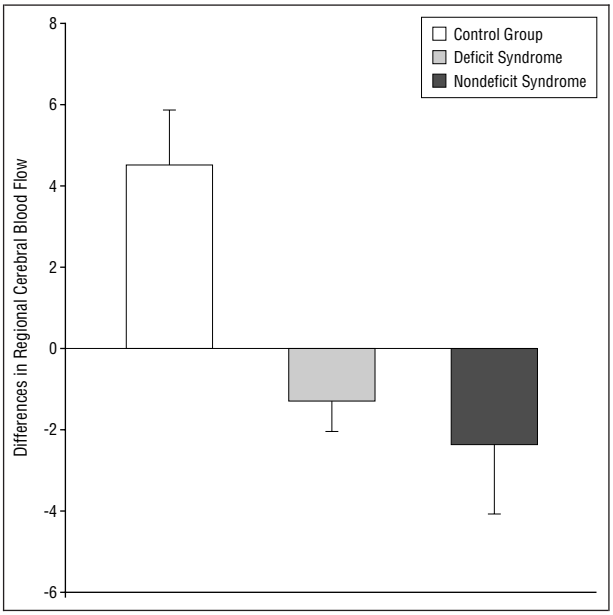

Figure 4. *Mean ± SEM differences in hippocampal recruitment (Δ regional cerebral blood flow) at coordinates 22, –28, –4 for the high-recall minus low-recall contrast between controls and the 2 schizophrenia subtypes (n = 8 for each group).*

COMMENT

Our study provides evidence that the frontal cortex is differentially impaired in deficit and nondeficit schizophrenia; frontal cortex activity during memory retrieval and left frontal cortex recruitment during retrieval attempt were significantly greater in patients with nondeficit syndrome. However, the medial temporal lobe is similarly impaired in deficit and nondeficit schizophrenia; both schizophrenia groups did not differ in medial temporal lobe activity and failed to exhibit the normal pattern of hippocampal recruitment during memory retrieval.

Recent functional neuroimaging studies have demonstrated that the prefrontal cortex and hippocampus are associated with distinct components of memory retrieval.[40-42] The right frontal cortex is consistently activated during intentional declarative or episodic retrieval of words, faces, scenes, or objects.[30,40,43-46] The degree of right frontal activation during intentional retrieval may reflect the degree of strategic monitoring of memory retrieval.[40,47-49] Hippocampal recruitment is associated with encoding and subsequent successful retrieval of memory.[30,31,41,50-52] The pattern of right prefrontal cortex and hippocampal activation in our control group[29] is consistent with these previous studies of memory retrieval.

Our results add new information to the existing literature regarding frontal and temporal lobe function in schizophrenia. Schizophrenia has long been associated with frontal lobe pathologic features.[53] More recently, the theory of hypofrontality in schizophrenia[4] has been advanced, based mainly on findings of structural and functional neuroimaging studies. However, the concept of hypofrontality has not remained unchallenged.[15,54] We found hypofrontality when comparing mean rCBF values across memory retrieval conditions; it was most pronounced in the patients with deficit syndrome. However, rCBF

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changes in prefrontal areas during memory retrieval were more variable. Furthermore, although the 2 schizophrenia groups differed in frontal cortex activity during memory retrieval, they did not differ in recall accuracy scores. This raises 2 questions: How does prefrontal cortex activity relate to task performance?[55] and Does a lower rCBF starting point provide greater capacity for rCBF increases?[15,56] To our knowledge, these issues have not yet been studied in schizophrenia.

Previous studies have reported differential impairment of cognitive function,[57-59] brain structure,[60] and brain function[61] in deficit and nondeficit schizophrenia. Two previous studies of cerebral glucose metabolism at rest have reported differential involvement of frontal and temporal areas in deficit vs nondeficit schizophrenia. Tamminga et al[61] reported cortical hypometabolism in patients with deficit syndrome only and hippocampal hypometabolism in patients with deficit syndrome and those with nondeficit syndrome. Gur et al[62] reported no differences in temporal lobe metabolism between deficit and nondeficit groups, but found increased left temporal metabolism in patients with negative symptoms as well as those with Schneiderian delusions and hallucinations. Differences in imaging methods (rest vs activation, metabolism vs blood flow, region-of-interest analysis vs SPM) make it difficult to compare our results with those in these 2 previous studies. However, the prominent involvement of the medial temporal lobe in both deficit and nondeficit schizophrenia and the decrease of frontal activity primarily in patients with negative symptoms is a consistent theme in all 3 studies.

Several authors have proposed that temporal lobe dysfunction is associated with delusions and hallucinations in schizophrenia[23,63-67] and in cases of organic psychosis.[68] Furthermore, abnormal frontal-temporal connections are proposed to give rise to schizophrenia.[69-73] Our study of memory retrieval provides evidence for differential dysfunction of the frontal-temporal neural network in patients with schizophrenia with and without the deficit syndrome.

We have to consider treatment with neuroleptic medication and small sample size as 2 limitations of our study. All patients with schizophrenia were stable outpatients, treated with typical neuroleptics; some were treated with anticholinergic drugs. This could have affected memory performance and rCBF. We decided to study stable patients given neuroleptic medication since drug discontinuation could have worsened hippocampal function and memory performance.[74] Furthermore, there is no evidence that long-term exposure to typical neuroleptics changes blood flow patterns in schizophrenia in the temporal lobe or in the prefrontal cortex during cognitive activation.[75,76] The findings from the direct comparison of patients with deficit syndrome and those with nondeficit syndrome are not confounded by age or duration of illness and are unlikely to be confounded by antipsychotic medication (various typical neuroleptics, similar chlorpromazine-equivalent doses). Although we studied small samples, we used a mixed-effects model in our analysis of the behavioral and PET data. This allows us to make inferences not only about the study samples, but also about the populations from which the samples were drawn.[77-79]

In summary, we found evidence for frontal and temporal lobe dysfunction in schizophrenia. Deficit and nondeficit schizophrenia differ in the degree of frontal lobe dysfunction during memory retrieval but are similarly impaired in hippocampal recruitment.

Accepted for publication August 20, 1999.

This study was supported by a Dupont-Warren Fellowship from Harvard Medical School, Boston, Mass (Dr Heckers); by Staglin Music Festival Investigator Award (Dr Heckers) and a Young Investigator Award (Dr Rauch) from the National Alliance for Research on Schizophrenia and Depression, Great Neck, NY; and by grants K20MH01215 (Dr Rauch) and R01MH57915 (Dr Schacter), from the National Institute of Mental Health, Rockville, Md.

We thank Dmitry Berdichevsky, MS, Zakhar Levin, MS, Avis Loring, RT, Sandra Barrow, BS, Steve Weise, BS, Ed Amico, MEd, and Dana Ruther, MA, for technical assistance.

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