Impaired recruitment of the hippocampus during conscious recollection in schizophrenia

Stephan Heckers[1,2], Scott L. Rauch[2,3], Donald Goff[1], Cary R. Savage[2], Daniel L. Schacter[4], Alan J. Fischman[3] and Nathaniel M. Alpert[3]

[1] *The Psychotic Disorders Unit and* [2]*The Psychiatric Neuroimaging Research Group, Department of Psychiatry, Massachusetts General Hospital, Boston, Massachusetts 02114, USA*

[3] *The Positron Emission Tomography Laboratory, Division of Nuclear Medicine, Department of Radiology, Massachusetts General Hospital, Boston, Massachusetts 02114, USA*

[4] *Department of Psychology, Harvard University, Cambridge, Massachusetts 02138, USA*

Correspondence should be addressed to S.H. (heckers@psych.mgh.harvard.edu)

Poor attention and impaired memory are enduring and core features of schizophrenia. These impairments have been attributed either to global cortical dysfunction or to perturbations of specific components associated with the dorsolateral prefrontal cortex (DLPFC), hippocampus and cerebellum. Here, we used positron emission tomography (PET) to dissociate activations in DLPFC and hippocampus during verbal episodic memory retrieval. We found reduced hippocampal activation during conscious recollection of studied words, but robust activation of the DLPFC during the effort to retrieve poorly encoded material in schizophrenic patients. This finding provides the first evidence of hippocampal dysfunction during episodic memory retrieval in schizophrenia.

Schizophrenia is typically associated with the occurrence of hallucinations and delusions. However, since the original description of the disorder as *dementia praecox*, cognitive deficits have been recognized as core features of the disease[1,2]. Inattention and memory impairment are especially enduring symptoms that often do not respond to treatment and contribute to poor prognosis and disability[3].

Functional neuroimaging is, arguably, the best tool to investigate the neural basis of the symptoms of schizophrenia[4,5]. Such studies have demonstrated three patterns of abnormal cerebral blood flow during cognitive activation. First, impairment of working memory and executive functions in schizophrenia have been associated with decreased blood flow in the dorsolateral prefrontal cortex (DLPFC)[6]. Second, cognitive dysmetria, the inability to receive and process information rapidly, has been associated with a dysfunction of prefrontal-thalamic-cerebellar circuitry[7]. Third, auditory hallucinations and the experience of psychotic symptoms have been associated with increased blood flow in medial temporal lobe, limbic and subcortical structures[8,9].

Recent studies have mapped the neuroanatomy of memory to a network of cortical and subcortical structures in the human brain[10,11]. This provides a foundation to test the hypothesis that schizophrenia is associated with perturbations of specific memory components. Two areas of particular interest in the study of schizophrenia, the DLPFC[12] and the hippocampal formation[13], are involved in the encoding, storage and retrieval of memory. Activation of the DLPFC has been associated with semantic processing during encoding and with the effort of retrieval[14,15]. Hippocampal activation has been associated with the detection of novelty, with the creation of associations during encoding and with the experience of conscious recollection[14–16].

We used a recently developed positron emission tomography (PET) experimental design[14] to study prefrontal and hippocampal function during episodic memory retrieval in schizophrenia. Prior to scanning, subjects studied a list of written words for either (a) a shallow encoding task that required counting the number of T-junctions in the letters of each word, which usually results in poor subsequent memory for those words ('low recall'), or (b) a deep encoding task that required counting the number of meanings for each word, which usually produces robust subsequent memory for those words ('high recall'). Subjects were then scanned and tested with a stem-cued recall test, in which they were given three-letter word beginnings and were asked to retrieve studied words. This allowed us to contrast the effort of retrieval with the process of successful retrieval. Based on previous studies[11,14,17,18], we predicted that activation of the prefrontal cortex would correspond with the effort of retrieval and that hippocampal and parahippocampal activation would occur during successful retrieval of memory. Consistent with our hypothesis, we found the predicted pattern of regional brain activation during memory retrieval in the control group. In contrast, the schizophrenic patients recruited the prefrontal cortex during the effort of retrieval but did not recruit the hippocampus during conscious recollection. This pattern of activation was associated with higher accuracy during low recall and lower accuracy during high recall in schizophrenics than in control subjects.

Results

Behavioral data

We analyzed the effects of group, condition and run on recall accuracy with a repeated-measures ANOVA using subject as

Table 1. Brain regions showing significantly increased activity during low recall in control subjects and schizophrenic patients and significant differences between groups.

Low Recall Minus Baseline		
Region (Brodmann areas)	***Z* score**	**Coordinates**
Control subjects		
L Prefrontal (8)	3.50	-28, 14, 40
R Prefrontal (8)	3.46	42, 18, 44
R Precuneus (31)	3.18	20, -62, 12
Schizophrenic patients		
R Prefrontal (11)	4.38	18, 42, -12
R Prefrontal (10)	4.36	28, 56, 0
	3.65	2, 54, 8
R Prefrontal (9)	4.07	24, 32, 36
R Parietal (7)	3.48	36, -64, 44
R Thalamus	3.10	4, -18, 4
Between-group comparisons		
Control subjects > *Schizophrenic patients*		
no regions		
Schizophrenic patients > *Control subjects*		
R Inferior Temporal (20)	3.18	30, -36, -16

random effect. As expected, deep encoding resulted in better recall than shallow encoding in both groups, that is, they remembered many more words during the high-recall task (controls, 0.76; schizophrenics, 0.61) than during the low-recall task (controls, 0.28; schizophrenics, 0.35; main effect of condition, $F(1,18) = 244.0$, $p < .0001$). The increment in recall accuracy was significantly different between the two groups as revealed by a significant group-by-condition interaction ($F(1,18) = 21.4$, $p < .0001$). This was due to lower accuracy of the schizophrenic patients compared to controls during high recall (*t*-test, $p = .009$) and higher accuracy of the schizophrenic patients compared to controls during low recall (*t*-test, $p = .02$). It is important to note that, although the magnitude of the increase was different for the two groups (*t*-test, $p < .001$), both groups showed significantly more accuracy in high recall than in low recall (paired *t*-tests, control group, mean percent change, 0.48, $p < .0001$; schizophrenia group, 0.26, $p<.0001$). No other main effect or interaction was significant.

To test whether the schizophrenic patients were more accurate than controls during low recall because they failed to follow the shallow, perceptual encoding strategy, we compared the accuracy of counting the correct number of T-junctions (for each set of 20 words). The correct number of T-junctions varied between 0 and 7 per word. Accuracy scores for counting T-junctions in controls (mean ± SD, 0.89 ± 0.06; range, 0.82–0.98) and schizophrenic patients (0.78 ± 0.18; 0.45–0.98) were not significantly different, but there was a trend toward a group difference (unpaired *t*-test, $p = 0.11$). To investigate this trend further, we studied the individual accuracy scores of the thirteen schizophrenic patients for counting T-junctions. The counting of T-junctions was markedly less accurate in three patients (case 6, 0.45; case 7, 0.50; case 9, 0.63) compared with the range of the other ten patients (0.78–0.98). The recall accuracy scores during the online test unit for these three patients were very close (case 6, 0.38; cases 7 and 9, 0.40) to the mean recall accuracy score of the patient group (0.35).

PET DATA

Regional brain activation associated with the effort to recall recently studied words was investigated with the contrast of relative regional cerebral blood flow (rCBF) during low recall minus baseline conditions (Table 1). Control subjects showed significant rCBF increases in bilateral prefrontal areas and right precuneus. Schizophrenic patients showed rCBF increases in right prefrontal areas, right parietal cortex and right thalamus. Comparing rCBF changes during the effort to recall previously studied words revealed that activation of only one region, in the right inferior temporal cortex, was greater in schizophrenic patients than in controls; no other differences were significant (Table 1).

Regional brain activation during the actual recollection of recently studied words was investigated with the contrast of rCBF during high recall minus low recall conditions (Table 2). Control subjects showed significant rCBF increases in predicted regions of the right hippocampus and parahippocampal gyrus, with additional increases in retrosplenial, occipital and temporal regions. The schizophrenic patients showed no significant rCBF changes in medial temporal lobe structures during conscious recollection, but did show significant activation in right prefrontal cortex. There were several significant between-group differences during conscious recollection. Normal subjects showed significantly greater rCBF increases in the right hippocampus (Fig. 1) and the right superior temporal gyrus, whereas schizophrenic patients showed significantly greater rCBF increases in right prefrontal cortex and in bilateral inferior parietal areas (Table 2). The high-recall-minus-baseline contrast revealed less robust hippocampal acti-

Table 2. Brain regions showing significantly increased activity during high recall in control subjects and schizophrenic patients and significant differences between groups.

High Recall Minus Low Recall		
Region (Brodmann areas)	**Z score**	**Coordinates**
Control subjects		
L Retrosplenial (29/30)	3.36	-8, -50, 20
R Parahippocampal (35/36)	3.27	26, -38, -8
R Hippocampal	3.21	24, -26, -4
L Occipital (17)	3.16	-16, -90, 4
R Superior Temporal (22/42)	3.13	52, -4, 8
R Occipital (18)	3.12	28, -84, -4
Schizophrenic patients		
R Prefrontal (45)	3.20	28, 30, 4
Between-group comparisons		
Control subjects > *Schizophrenic patients*		
R Hippocampal	3.66	24, -28, -4
R Superior Temporal Gyrus (22/42)	3.12	56, -2, 8
Schizophrenic patients > *Control subjects*		
R Inferior Parietal (40)	3.60	48, -62, 40
R Prefrontal (10)	3.40	26, 48, 24
L Inferior Parietal (40)	3.21	-40, -46, 44

vation (coordinates 24, -28, -4; z = 1.81) in the control group, but between-group comparisons again revealed less hippocampal activation during conscious recollection in the schizophrenia group (coordinates 26, -28, -4; z = 2.38).

We further analyzed the finding of poor hippocampal activation during conscious recollection in schizophrenia, using a random-effects model (see Methods) to compare rCBF during the three conditions between the two groups and to retest the group-by-condition interaction. The control subjects showed significantly higher rCBF in bilateral frontal areas during all three conditions (baseline, low recall and high recall). The schizophrenic patients showed significantly higher rCBF in bilateral temporal, parietal, and occipital areas during all three conditions. Between-group analysis of the average of all three conditions (contrast 1,1,1,-1,-1,-1 and the reverse) revealed higher rCBF in multiple frontal areas in controls and higher rCBF in occipital, parietal and temporal areas, including the hippocampus (at coordinates 24, -28, -4, run 1, z = 6.31, run 2, z = 5.25), in schizophrenics. The group-by-condition interaction (i.e., hippocampal rCBF increased significantly more in the control group during conscious recollection) was confirmed in the random-effects model, using only one run per condition (contrast high1 - low1 (24, -28, -4) z = 2.75; contrast high2 - low2 (28, -32, -8) z = 2.85).

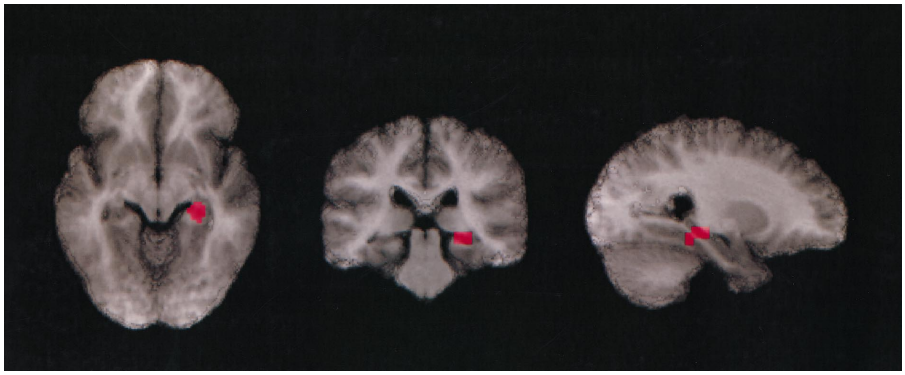

Fig. 1. PET statistical map comparing the contrast (high recall minus low recall) between control subjects and schizophrenic patients. The PET image is co-registered with an average normal magnetic resonance image (MRI), transformed to Talairach space. The three slices are at the level of the medial temporal lobe (horizontal level -4 mm, coronal level -28 mm and sagital level 24 mm in Talairach space). Compared with the control group, the right hippocampal region (at coordinates 24, -28, -4) was significantly less activated (p < .001, z > 3.09) in the schizophrenia group.

Further analysis of right hippocampal rCBF during low recall and high recall focused on nine contiguous voxels centered in coordinates 24, -28, -4, which is the region that was most significantly different between the two groups. Mean hippocampal rCBF was higher in the schizophrenia group compared with the control group during baseline and during low recall (Fig. 2a). Compared to low recall, hippocampal rCBF increased significantly (paired t-test, p = .013) during high recall in the control subjects (Fig. 2a), whereas the schizophrenic patients showed a nonsignificant decline. Hippocampal rCBF increased during high recall in seven of eight control subjects but in only one schizophrenic patient (Fig. 2b). The schizophrenic patient who showed hippocampal rCBF increases was only marginally more accurate at high recall (35% correct) than at low recall (28% correct).

Discussion

Memory retrieval in normal subjects

The activation of prefrontal areas, precuneus, medial temporal lobe, superior temporal gyrus and visual areas that we observed during episodic memory retrieval in our control group is consistent with previous reports[11,14,17,19–22]. As in our previous studies[14,17], we found that replacing a perceptual with a semantic encoding strategy increased recall accuracy, and that recollection of semantically encoded words was associated with right hippocampal activation. We have proposed[14] that prefrontal cortex activation during the low-recall condition reflects the effortful aspects of retrieval search and that hippocampal activation reflects a conscious recollective process. We had found in a previous study[17] that, in comparison with young adults, elderly control subjects perform less accurately and recruit farther posterior frontal areas during low recall. The control group in this study, whose age (mean, 40.0 years) was intermediate between the younger and older adults in our previous study, also activated farther posterior prefrontal areas. Moreover, they achieved recall accuracy scores during low recall similar to those of the elderly adults studied previously.

Memory retrieval in schizophrenic patients

During the low-recall condition, the schizophrenic patients showed increased rCBF in right parietal cortex (area 7), in right prefrontal areas (areas 9, 10 and 11) and in the right thalamus. Compared to the activation of one prefrontal area (area 8) in the control group, the schizophrenic patients activated several prefrontal areas that were located farther anterior. The more widespread activation of prefrontal areas might be related to greater effort by the patients throughout the experiment: they achieved higher recall accuracy during low recall and showed more activation of area 10 in the high-recall-minus-low-recall contrast (Table 2).

The schizophrenic patients were less accurate when they were required to use a higher-level semantic encoding and search strategy and did not show hippocampal recruitment during conscious recollection. In contrast, schizophrenic patients showed significant activation of regions that are associated with attention (area 40) and retrieval effort (area 10) during conscious recollection (Table 2). The activation of extrahippocampal areas associated with memory retrieval might represent the effort to compensate for the failed recruitment of the hippocampus, which produces variable outcomes.

Surprisingly, the schizophrenic patients performed more accurately than the controls during the low-recall condition. This indicates that they might have used ancillary strategies, during either encoding or retrieval, or both, to enhance their performance. As outlined above, the more widespread prefrontal cortex activation in the low-recall-minus-baseline contrast might indicate greater effort during recall in the schizophrenia group, explaining, at least in part, their higher accuracy.

We can only speculate about possible differences during encoding, as we do not have PET data from the study phase. The analy-

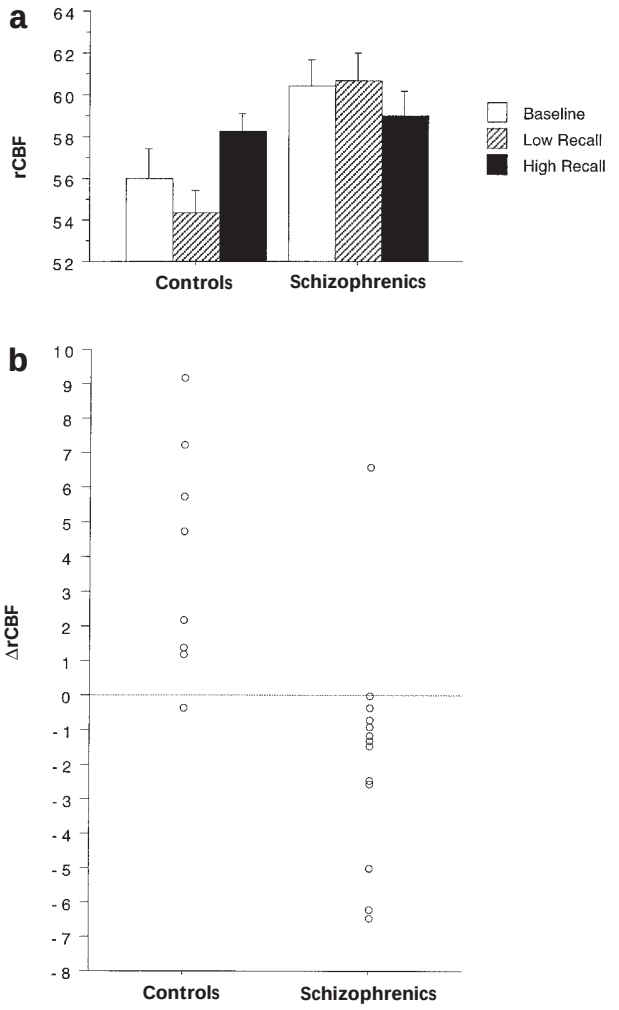

Fig. 2. Hippocampal rCBF during the three test conditions. **(a)** Means (and standard errors) of relative rCBF during baseline, low-recall and high-recall conditions from nine contiguous voxels centered in the right hippocampus voxel (24, -28, -4) that was most significantly different between the control and schizophrenia groups. **(b)** Difference of rCBF values between high recall and low recall in control subjects and schizophrenic patients. Seven out of eight controls, but only one out of thirteen schizophrenic patients, showed an increase in hippocampal rCBF during high recall.

sis of the patients' accuracy of counting T-junctions demonstrated that most patients performed well and followed the encoding instructions. However, schizophrenic patients might have used an additional deeper, possibly semantic, strategy to encode words from the low-recall study list. This could have occurred with the subject's awareness (explicit) or without (implicit). The observation that the patients performed poorly when instructed to employ an explicit semantic encoding strategy (high recall) makes an implicit strategy more likely. One possible mechanism is the failure to inhibit the creation of semantic associations during encoding, resulting in better performance at test. This hypothesis is consistent with previous studies showing that schizophrenic patients use automatic rather than voluntary processes to improve memory performance[23] and that they have impaired recognition memory with, but not without, conscious recollection[24].

Another explanation can be derived from our finding of high hippocampal rCBF in all three word-stem-completion conditions. Compared to the control group, hippocampal activity was continuously increased in schizophrenia and was not modulated by environmental contingencies. Such uncontrolled hippocampal activation might improve memory processes that do not normally recruit the hippocampus (e.g., effortful retrieval search, priming) and perturb those that depend on the hippocampus. This explanation is consistent with theoretical models of hippocampal hyperactivity causing abnormal thought processes, hallucinations and delusions in schizophrenia[25,26].

Hippocampal dysfunction in schizophrenia

Our finding of hippocampal dysfunction during episodic memory retrieval in schizophrenia complements recent evidence of abnormal hippocampal structure and function in schizophrenia[9,13,27–29]. Our study demonstrates that hippocampal hyperactivity is present in schizophrenia not only at rest[8,30–32] but also during cognitive activation (baseline and low recall) that interferes with the normal recruitment of the hippocampus during memory retrieval. Functional hyperactivity in the setting of structural deficits of the hippocampus in schizophrenia has been interpreted as reduced efficiency of transsynaptic activity[31]. It is unlikely that hippocampal rCBF in our sample of schizophrenic patients was at a maximum that could not be increased, because area 40 also showed significantly higher rCBF at baseline in the schizophrenia group but still showed significantly greater rCBF increases during task performance. Increased hippocampal activity at baseline and impaired recruitment during episodic memory retrieval might represent the functional correlate of an abnormal corticohippocampal interaction in schizophrenia[29,31,33,34].

Limitations and conclusions

The patient sample consisted of middle-aged males with predominantly hallucinatory symptoms and a disease onset before age 40. Previous studies have not found significant correlations of age, chronicity or sex with memory dysfunction in schizophrenia[35]. However, schizophrenia is heterogeneous, and future studies are necessary to replicate our findings in a larger sample and across the different subtypes of the disease.

All patients were chronically treated with typical neuroleptic medication, and four patients were chronically treated with anticholinergic medication. Like others[36], we found no correlation between correct response rates and neuroleptic dose in our sample (Spearman rank correlation, high recall rho -.18, $p = 0.58$; low recall rho .09, $p = 0.79$). There is no evidence that chronic exposure to typical neuroleptics changes blood-flow patterns in schizophrenia in the temporal lobe[37] or in the DLPFC during cognitive activation[6,36] . In fact, it is likely that discontinuation of chronic neuroleptic treatment would have worsened hippocampal function and memory performance in our sample[38]. We have to consider a salutary effect of neuroleptic treatment on vigilance and attention, which should have improved overall task performance and is an unlikely explanation for the dissociation of prefrontal and hippocampal activation that we found.

Our study provides the first evidence of impaired hippocampal function in schizophrenia during episodic memory retrieval. The pattern of increased hippocampal blood flow at baseline and abnormal recruitment during conscious recollection indicates a failure to modulate hippocampal activity

based on contingencies of the environment. Hippocampal dysfunction might also be involved in the production of psychotic symptoms in schizophrenia[8,9,31,39], contributing to poor prognosis and inadequate response to treatment.

Methods

SUBJECTS. Thirteen schizophrenic patients and eight psychiatrically normal control subjects, all without any history of neurological illness, were studied using a recently developed positron emission tomography approach[14]. Diagnoses were made using a structured clinical interview[40]. Eight patients were diagnosed as paranoid-hallucinatory and five as undifferentiated subtype of schizophrenia, according to DSM-IV criteria[41].

Mean duration of illness was 18.2 ± 6.1 years. Mean scores on the positive, negative and global scales of the positive and negative syndrome scale (PANSS)[42] were 15.2 ± 5.6, 18.9 ± 3.3 and 28.6 ± 4.8, respectively. All subjects were right-handed males, and both groups were matched for age (normal subjects 40.0 ± 6.3 years, schizophrenic patients 41.7 ± 5.8 years). The control subjects had a higher educational status (control subjects 14.9 ± 1.1 years, schizophrenic patients 13.1 ± 2.3 years, $p = .05$, t-test), but mean parental educational status was not significantly different (control subjects 12.6 ± 2.7 years, schizophrenic patients 11.4 ± 2.1 years, $p = .28$, t-test). All patients were treated with typical neuroleptics (mean chlorpromazine equivalent dose 377 mg per day, range 50–800 mg per day). Four patients were treated with benztropine (1–2 mg per day; they ranked 1st, 5th, 7th and 11th for mean performance scores in the schizophrenic sample).

EXPERIMENTAL DESIGN. Subjects underwent six scans. During scans one and six, subjects were instructed to complete three-letter word stems presented on the computer screen into the first word that came to mind (baseline condition). Two pairs of scans (scans two and three and scans four and five) followed after two offline study sessions. During the study session, subjects were presented with a randomized list of 100 target words, composed of 20 words presented once and 20 words presented four times. The subjects were instructed to count T-junctions in the target words presented once (perceptual encoding strategy) and to count meanings of the target words presented four times (semantic encoding strategy). We gave very specific instructions before each encoding block to count either T-junctions or the number of meanings of the word presented on the screen. All subjects successfully completed an offline trial to ensure that they were able to follow the instructions. During scanning, the subjects were asked to complete three-letter word stems of words presented either once (low-recall condition) or four times (high-recall condition). The order of the scanned recall sessions (two runs of each condition) was counterbalanced across subjects.

PET SCANNING. PET data were acquired with a General Electric-Scanditronix PC4096 15-slice whole body tomograph. Subjects underwent six one-minute scans and inhaled [^{15}O]CO_2 gas beginning 30 seconds after the initiation of the task. Subjects performed tasks while viewing a computer screen and responded verbally. PET images were reconstructed with a conventional convolution-backprojection algorithm, corrected for photon absorption, scatter and dead-time effects.

DATA ANALYSIS. Realignment of images and transformation into the standard stereotactic space of Talairach was performed as described[43]. Images were smoothed with a two-dimensional Gaussian filter of width 15 mm FWHM. Within-group analyses and initial between-group analyses were performed using SPM95 (Wellcome Dept. of Cognitive Neurology, London, UK). Main effects and interactions were assessed with two contrasts (low recall minus baseline and high recall minus low-recall), using t statistics subsequently transformed into normally distributed z scores. Statistical parametric maps were thresholded at an uncorrected $p < .001$ (i.e., $z > 3.09$). Further between-group analyses were performed with a random-effects model in the SPM95 environment[44]. The data were modeled with explanatory variables for group and condition (no block effect), with one scan per condition. This allowed the comparison of rCBF in one condition across groups, rather than the comparison of relative rCBF changes between two conditions across groups as implemented in SPM95. Additional region-of-interest analysis used the individual rCBF values at the peak of hippocampal activation in the SPM, divided by the individual global cerebral blood flow and multiplied by 50.

Acknowledgments

The authors thank Dmitry Berdichevsky, Zakhar Levin, Avis Loring, Steve Weise, Ed Amico and Dana Ruther for technical support. This study was supported by a Dupont-Warren Fellowship (S.H.), a Young Investigator Award from the National Alliance for Research on Schizophrenia and Depression (S.L.R.) and NIMH grants R01MH57915 (D.L.S.) and MH01215 (S.L.R.).

RECEIVED 27 MARCH; ACCEPTED 8 JUNE 1998

1. Kraepelin, E. *Dementia Praecox and Paraphrenia* (Livingstone, Edinburgh, 1919).
2. Goldberg, T. E. & Gold, J. M. in *Schizophrenia* (eds Hirsch, S. R. & Weinberger, D. R.) 146–162 (Blackwell Science Ltd, Oxford, 1995).
3. Green, M. F. What are the functional consequences of neurocognitive deficits in schizophrenia? *Am. J. Psychiatry* 153, 321–330 (1996).
4. Andreasen, N. C. Pieces of the schizophrenia puzzle fall into place. *Neuron* 16, 697–700 (1996).
5. Andreasen, N. C. Linking mind and brain in the study of mental illnesses: a project for a scientific psychopathology. *Science* 275, 1586–1593 (1997).
6. Berman, K. F., Zec, R. F. & Weinberger, D. R. Physiologic dysfunction of dorsolateral prefrontal cortex in schizophrenia. II. Role of neuroleptic treatment, attention, and mental effort. *Arch. Gen. Psychiatry* 43, 126–135 (1986).
7. Andreasen, N. C. *et al.* Schizophrenia and cognitive dysmetria: A positron-emission tomography study of dysfunctional prefrontal-thalamic-cerebellar circuitry. *Proc. Natl. Acad. Sci. USA* 93, 9985–9990 (1996).
8. Liddle, P. F. *et al.* Patterns of cerebral blood flow in schizophrenia. *Br. J. Psychiatry* 160, 179–186 (1992).
9. Silbersweig, D. A. *et al.* A functional neuroanatomy of hallucinations in schizophrenia. *Nature* 378, 176–179 (1995).
10. Ungerleider, L. G. Functional brain imaging studies of cortical mechanisms for memory. *Science* 270, 769–775 (1995).
11. Fletcher, P. C., Frith, C. D. & Rugg, M. D. The functional neuroanatomy of episodic memory. *Trends Neurosci.* 20, 213–218 (1997).
12. Goldman-Rakic, P. S. & Selemon, L. D. Functional and anatomical aspects of prefrontal pathology in schizophrenia. *Schizophrenia Bull.* 23, 437–458 (1997).
13. Arnold, S. E. The medial temporal lobe in schizophrenia. *J. Neuropsychiatry Clin. Neurosci.* 9, 460–470 (1997).
14. Schacter, D. L., Alpert, N. M., Savage, C. R., Rauch, S. L. & Albert, M. S. Conscious recollection and the human hippocampal formation: evidence from positron emission tomography. *Proc. Natl. Acad. Sci. USA* 93, 321–325 (1996).
15. Dolan, R. J. & Fletcher, P. C. Dissociating prefrontal and hippocampal function in episodic memory encoding. *Nature* 388, 582–585 (1997).
16. Henke, K., Buck, A., Weber, B. & Wieser, H. G. Human hippocampus establishes associations in memory. *Hippocampus* 7, 249–256 (1997).
17. Schacter, D. L., Savage, C. R., Alpert, N. M., Rauch, S. L. & Albert, M. S. The role of hippocampus and frontal cortex in age-related memory changes: a PET study. *Neuroreport* 7, 1165–1169 (1996).
18. Nyberg, L., McIntosh, A. R., Houle, S., Nilsson, L.-G. & Tulving, E. Activation of medial temporal structures during episodic memory retrieval. *Nature* 380, 715–717 (1996).
19. Squire, L. R. *et al.* Activation of the hippocampus in normal humans: a functional anatomical study of memory. *Proc. Natl. Acad. Sci. USA* 89, 1837–1841 (1992).
20. Tulving, E., Kapur, S., Craik, F. I. M., Moscovitch, M. & Houle, S. Hemispheric encoding/retrieval asymmetry in episodic memory: positron emission tomography findings. *Proc. Natl. Acad. Sci. USA* 91, 2016–2020 (1994).
21. Buckner, R. L. *et al.* Functional anatomical studies of explicit and implicit memory retrieval tasks. *J. Neurosci.* 15, 12–29 (1995).
22. Schacter, D. L. *et al.* Neuroanatomical correlates of veridical and illusory recognition memory: evidence from positron emission tomography. *Neuron* 17, 267–274 (1996).
23. Spitzer, M., Braun, U., Hermle, L. & Maier, S. Associative semantic network dysfunction in thought-disordered schizophrenic patients: direct evidence from indirect semantic priming. *Biol. Psychiatry* 34, 864–877 (1993).
24. Huron, C. *et al.* Impairment of recognition memory with, but not without, conscious recollection in schizophrenia. *Am. J. Psychiatry* 152, 1737–1742 (1995).

25. Venables, P. H. Hippocampal function and schizophrenia. Experimental psychological evidence. *Ann. NY Acad. Sci.* 658, 111–127 (1992).
26. Krieckhaus, E. E., Donahoe, J. W. & Morgan, M. A. Paranoid schizophrenia may be caused by dopamine hyperactivity of CA1 hippocampus. *Biol. Psychiatry* 31, 560–570 (1992).
27. Dwork, A. J. Postmortem studies of the hippocampal formation in schizophrenia. *Schizophrenia Bull.* 23, 403–421 (1997).
28. Beauregard, M. & Bachevalier, J. Neonatal insult to the hippocampal region and schizophrenia: a review and a putative animal model. *Can. J. Psychiatry* 41, 446–456 (1996).
29. Weinberger, D. R., Berman, K. F., Suddath, R. & Torrey, E. F. Evidence of dysfunction of a prefrontal-limbic network in schizophrenia: a magnetic resonance imaging and regional cerebral blood flow study of discordant monzygotic twins. *Am. J. Psychiatry* 149, 890–897 (1992).
30. DeLisi, L. E. *et al.* Increased temporal lobe glucose use in chronic schizophrenic patients. *Biol. Psychiatry* 25, 835–851 (1989).
31. Friston, K. J., Liddle, P. F., Frith, C. D., Hirsch, S. R. & Frackowiak, R. S. The left medial temporal region and schizophrenia. A PET study. *Brain* 115, 367–382 (1992).
32. Kawasaki, Y. *et al.* Regional cerebral blood flow in patients with schizophrenia: relevance to symptom structures. *Psychiatry Res.* 67, 49–58 (1996).
33. Frith, C. D. *et al.* Regional brain activity in chronic schizophrenic patients during the performance of a verbal fluency task. *Br. J. Psychiatry* 167, 343–349 (1995).
34. Goldman-Rakic, P. S. Working memory dysfunction in schizophrenia. *J. Neuropsychiatry Clin. Neurosci.* 6, 348–357 (1994).
35. Heaton, R. *et al.* Neuropsychological deficits in schizophrenics. Relationship to age, chronicity, and dementia. *Arch. Gen. Psychiatry* 51, 469–476 (1994).
36. Goldberg, T. E. & Weinberger, D. R. Effects of neuroleptic medication on the cognition of patients with schizophrenia: a review of recent studies. *J. Clin. Psychiatry* 57 [suppl 9], 62–65 (1996).
37. Miller, D. D., Rezai, K., Alliger, R. & Andreasen, N. C. The effect of antipsychotic medication on relative cerebral blood perfusion in schizophrenia: assessment with technetium-99m hexamethyl-propyleneamine oxime single photon emission computed tomography. *Biol. Psychiatry* 41, 550–559 (1997).
38. Gilbertson, M. W. & van Kammen, D. P. Recent and remote memory dissociation: medication effects and hippocampal function in schizophrenia. *Biol. Psychiatry* 42, 585–595 (1997).
39. Tamminga, C. A. *et al.* Limbic system abnormalities identified in schizophrenia using positron emission tomography with fluorodeoxyglucose and neocortical alterations with deficit syndrome. *Arch. Gen. Psychiatry* 49, 522–530 (1992).
40. Spitzer, R. L., Williams, J. B. W., Gibbon, M. & First, M. B. *Structured clinical interview for DSM-III-R.* (American Psychiatric Press, Washington, DC, 1991).
41. *Diagnostic and Statistical Manual of Mental Disorders, 4th edition*. pp 273–290 (American Psychiatric Association, Washington, DC, 1994).
42. Kay, S. R., Fiszbein, A. & Opler, L. A. The Positive and Negative Syndrome Scale (PANSS) for schizophrenia. *Schizophrenia Bull.* 13, 261–276 (1987).
43. Alpert, N. M., Berdichevsky, D., Levin, Z., Morris, E. D. & Fishman, A. J. Improved methods for image registration. *Neuroimage* 3, 10–18 (1996).
44. Woods, R. P. Modeling for intergroup comparisons of imaging data. *Neuroimage* 4, S84–S94 (1996).