Impaired Hippocampal Recruitment during Normal Modulation of Memory Performance in Schizophrenia

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Background: *Patients with schizophrenia demonstrate poor verbal memory, ascribed to impaired prefrontal and hippocampal function. Healthy adults can increase recall accuracy following encoding interventions, such as item repetition and the formation of semantic associations. We examined the effects of these interventions on both memory performance and retrieval-related hippocampal activity in healthy adults and patients with schizophrenia.*

Methods: *Twelve patients with schizophrenia and twelve healthy control subjects participated. During study, subjects counted either the number of meanings or T-junctions in words seen only once or repeated four times. At test, O^{15}–positron emission tomography scans were acquired while subjects completed word-stems with previously studied items.*

Results: *Control subjects recalled more words overall, but both groups demonstrated similar performance benefits following deeper encoding. Both item repetition and the use of a semantic encoding task were associated with memory retrieval–related hippocampal recruitment in control but not schizophrenic participants. Patients with schizophrenia demonstrated greater activation of prefrontal cortical areas during word retrieval.*

Conclusions: *Despite a lack of hippocampal recruitment, patients with schizophrenia showed intact modulation of memory performance following both encoding interventions. Impaired hippocampal recruitment, in concert with greater prefrontal activation, may reflect a specific deficit in conscious recollection in schizophrenia.* Biol Psychiatry 2003;53:48–55 © *2003 Society of Biological Psychiatry*

Key Words: Schizophrenia, memory, hippocampus, positron emission tomography, functional neuroimaging, cognitive remediation

Introduction

Memory impairment is an often unrecognized but debilitating aspect of the schizophrenia syndrome (Aleman et al 1999). As memory performance is the best predictor of overall psychosocial well-being in patients with schizophrenia (Green 1996; Green et al 2000), understanding the neural basis of memory dysfunction is critical in effecting better functional outcomes for patients with this disorder.

Although the neural underpinnings of impaired memory in schizophrenia are incompletely understood, most evidence implicates aberrant activity in two brain regions critical for normal memory: the hippocampus and the dorsolateral prefrontal cortex (Weiss and Heckers 2001). Our previous work, for example, demonstrated impaired recruitment of the hippocampus in schizophrenic patients performing a word-stem retrieval memory paradigm (Heckers et al 1998). This study examined the impact of a dual encoding manipulation (item repetition and performing a semantic encoding task) on subsequent recall success and retrieval-related hippocampal activation. Control subjects showed a substantial benefit in memory retrieval following this combined encoding manipulation, with nearly a three-fold increase in memory retrieval. Patients with schizophrenia, though showing some improvement in memory after deep encoding, did not benefit as much from this intervention. In the control subjects, the improved memory retrieval following deep encoding was associated with greater activity in the right hippocampus. Patients with schizophrenia failed to recruit this region, instead showing greater activation in prefrontal cortical areas. We interpreted the lack of hippocampal recruitment as a sign of impaired conscious recollection of deeply encoded words, and the greater prefrontal activation as evidence of greater retrieval effort, used as a compensatory mechanism to improve memory performance.

The present study aimed to examine further these deficits in modulation of memory performance and hippocampal activity. Our previous study combined two encoding manipulations to produce a "high recall" and "low recall" condition. The high recall condition consisted

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Table 1. Characteristics of Schizophrenia and Control Subjects

	Schizophrenia (n = 12)	Control (n = 12)	t	p
Age (y)	47.8 (6.1)	48.8 (10.5)	.29	ns
Mean parental education (y)	12.8 (2.7)	12.7 (1.5)	−.09	ns
Education (y)	12.1 (3.4)	14.9 (3.5)	2.02	.056
Socioeconomic status[a]	2.6 (.9)	2.7 (.8)	.11	ns
Estimated IQ[b]	98 (13)	112 (12)	2.79	<.05
Positive and Negative Syndrome Scale	58.5 (9.6)	—	—	—
Scale for the Assessment of Negative Symptoms	38.3 (8.6)	—	—	—
Simpson-Angus Rating Scale[c]	3.1 (3.3)	—	—	—
Abnormal Involuntary Movement Scale[d]	2.6 (1.0)	—	—	—

Values are given as means (SD). Statistical comparisons used Student's t test. IQ, intelligence quotient.
[a]Measured using the Hollingshead index.
[b]Measured using the North American Adult Reading Test.
[c]Assesses extrapyramidal symptoms.
[d]Assesses tardive dyskinesia.

of items encoded four times while performing a semantic task (counting the number of meanings of the word), whereas the low recall condition consisted of items seen only once, encoded using a perceptual task (counting the number of T-junctions that occur within a word). We created a novel 2 × 2 factorial design, to create four distinct levels of recall success. By teasing apart the two encoding manipulations used in the previous experiment, we were now also able to specifically examine the effect of a semantic encoding task on memory recall in schizophrenia; this is of particular interest given the known deficits in the use of associative encoding seen in this disorder (Brebion et al 1997; Chan et al 2000; Ragland et al 2001). Using this design, we recently found that healthy control subjects improved recall performance following both word repetition and the use of a semantic encoding strategy, and that these increases in recall accuracy are associated with greater hippocampal activation (Heckers et al 2002). We hypothesized that patients with schizophrenia would not benefit as much from these encoding manipulations and would not demonstrate the normal pattern of retrieval-associated hippocampal recruitment.

Methods and Materials

Subjects

Twelve male patients with DSM-IV–defined schizophrenia were recruited from the outpatient Psychotic Disorders Clinic of the Massachusetts General Hospital. All diagnoses were confirmed using the Structured Clinical Interview for DSM-IV (SCID; First et al 1995), administered by clinic psychiatrists. The mean duration of illness was 23 (SD = 9) years. All patients were taking a stable dose of antipsychotic medication (four on conventional neuroleptics [mean dose equivalent to 384 mg of chlorpromazine], eight on atypical neuroleptics) and were not withdrawn from their medication for the purposes of the study. In addition, four of the patients were taking anticholinergic medication (benztropine or trihexyphenidyl) at the time of the study participation. Patients were excluded if they had a history of significant neurologic illness (seizure disorder, head trauma, stroke) or met criteria for alcohol or other substance abuse within the previous 3 months.

Twelve age-matched male subjects, recruited via advertisement from the local community, served as a control group. Control subjects were free of any Axis I psychiatric condition, as determined by SCID (administered by APW) and did not have a history of major medical or neurologic illness. None of the control subjects was taking psychotropic medication.

There were no significant differences in age, mean parental education level, or socioeconomic status between the patient and control groups (Table 1). Control subjects had attained higher levels of formal education, though this did not reach statistical significance (p = .056). Estimated intelligence quotient (IQ), as determined by the North American Adult Reading Test (Blair and Spreen 1989), was significantly greater in the control subjects (112 ± 12) than in the patients with schizophrenia (98 ± 13) [$t(22) = 2.79$, $p < .05$].

Before enrollment of subjects, the protocol was approved by the Institutional Review Board of the Massachusetts General Hospital and the Central Office Research Review Committee of the Commonwealth of Massachusetts, Department of Mental Health. Informed, written consent was obtained from all participants, following a complete description of the study.

Experimental Design

All subjects underwent eight positron emission tomography (PET) scans while inhaling [^{15}O] CO_2 gas. An Apple G3 Powerbook computer (Apple Computer, Cupertino, CA) presented the stimuli within a 6-inch × 6-inch area in the center of the screen, positioned approximately 50 cm from the prone subject. Scans 1 and 8 served as a "low-level" baseline, consisting of simply viewing a "white noise" visual image of scattered dots (Martin 1999). During scans 2 and 7, subjects were asked to complete 20 three-letter word-stems into the first word that came to mind ("active baseline") by responding verbally. Word-stems

appeared in all capital letters, in a 72-point Geneva font, and were presented for 5 sec apiece.

Scans 3–6 comprised the word-stem retrieval memory paradigm. Before scans 3 and 5 there was a study period, during which subjects were presented with a randomized list of 100 target words: 20 words presented once and 20 words presented four times. In one block, subjects were asked to count the number of meanings of the words presented in quadruplicate (semantic encoding) and count the number of T-junctions (defined as a perpendicular crossing within individual letters) in the words presented only once (perceptual encoding). In the other study block, the instructions were reversed, thereby producing four separate conditions in a 2 × 2 factorial design: Semantic 4×, Semantic 1×, Perceptual 4×, and Perceptual 1×. Word lists were rotated among the four conditions (and two active baselines) in a counterbalanced fashion. The order of the scanned recall sessions was also counterbalanced across subjects.

Each word was presented for 5 sec, and responses (number of T-junctions or meanings) were given verbally by the subject. During the subsequent memory retrieval tasks (scans 3–6) subjects were asked to complete a three-letter word stem with a target word by responding verbally during a 5-sec period. Subjects were encouraged to provide an answer, giving their "best guess" if uncertain.

PET Scan Acquisition

Positron emission tomography scans were acquired with a Scanditronix PC4096 (General Electric, Milwaukee, WI) 15-slice, whole-body tomograph. The slice geometry consisted of contiguous slices with center-to-center distance of 6.5 mm (axial field equal to 97.5 mm) and axial resolution of 6.0 mm full-width half maximum (FWHM). Images were reconstructed using a computed attenuation correction and a Hanning-weighted reconstruction filter set to yield 8.0-mm, in-plane, spatial resolution FWHM. Additional corrections were made to account for photon absorption, scatter, and dead-time effects.

Subjects were positioned in the scanner with an individually molded thermoplastic mask to minimize head motion. Head alignment was made relative to the canthomeatal line to ensure maximal coverage of prefrontal areas and complete coverage of the medial temporal lobes. Transmission measurements were made using an orbiting pin source. Subjects underwent 1-min scans inhaling [^{15}O] CO_2 gas delivered via a facemask positioned snugly over the nose and mouth 30 sec after the initiation of the task. Each scan was followed by a 10-min washout period.

Data Analysis

Memory performance was analyzed using a repeated-measures analysis of variance (ANOVA), with diagnosis (schizophrenia vs. control) as a between-subject factor and encoding task (semantic vs. perceptual) and item repetition (4× vs. 1×) as within-subject factors.

Positron emission tomography images were analyzed using statistical parametric mapping (SPM 99, Wellcome Department of Cognitive Neurology, London, UK). Images were realigned and transformed into standard Talairach space, then smoothed using a two-dimensional, 15-mm, FWHM Gaussian filter. Planned contrasts followed the 2 × 2 factorial design described above: within-group analyses assessed the main effects of repetition (4× vs. 1×) and encoding task (semantic vs. perceptual) and between-group analyses assessed the group × condition interactions. We employed a random-effects model, with statistical parametric maps thresholded at an uncorrected $p < .001$ ($z = 3.09$) for the *a priori* regions of interest in the hippocampus and prefrontal cortex. Statistical significance in all other voxels outside these *a priori* defined regions was set at a $p < .05$, corrected for multiple comparisons.

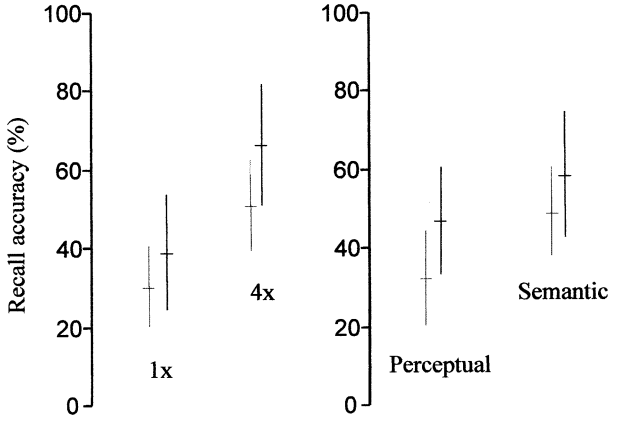

Figure 1. Behavioral data. Improved word-stem cued recall accuracy scores (means ± SD) in both patients with schizophrenia (gray lines) and control subjects (black lines) following repeated (4×) word encoding and the use of a semantic (as compared to perceptual) encoding task.

Results

Behavioral Performance

Control subjects recollected a significantly greater percentage of words (mean across all conditions = 53 ± 14%) than the patients with schizophrenia (41 ± 10%) [main effect of diagnosis: $F(1,22) = 5.9$, $p < .05$]. Repetition of study items at encoding significantly improved subsequent recall in both groups [main effect of repetition: $F(1,22) = 135.8$, $p < .0001$]. Similarly, the use of a semantic (as compared with perceptual) encoding task increased recall accuracy in both groups [main effect of encoding task: $F(1,22) = 37.7$, $p < .0001$]. The repetition of study items had a greater impact on subsequent recall when engaging a semantic, as compared with perceptual, encoding task [$F(1,22) = 24.5$, $p < .0001$]. There were no significant diagnosis × encoding condition interactions (i.e., patients showed similar modulation of performance across task conditions as the control subjects) (Figure 1).

To assess whether simple inattention or failure to engage in encoding processes might account for the overall performance discrepancy between the two groups,

Table 2. Brain Regions Showing Significantly Increased Activity during Retrieval

Region (Brodmann area)	*Z* score	Coordinates x	y	z
Main effect of encoding task: semantic > perceptual				
Control subjects				
Right hippocampus	3.49	26	−28	−6
Schizophrenic subjects				
Left prefrontal cortex (47)	3.48	−44	30	−16
Left prefrontal cortex (10)	3.29	−6	60	−2
Main effect of repetition: 4× > 1×				
Control subjects				
Left hippocampus	3.44	−32	−16	−16
Schizophrenic subjects				
Right prefrontal cortex (9/10)	3.31	4	58	16

Table 3. Significant Group Differences of Brain Activity during Retrieval

Region (Brodmann area)	*Z* score	Coordinates x	y	z
Between-group comparison: semantic > perceptual				
Control > schizophrenic				
Right medial temporal lobe	3.64	28	−12	−6
Schizophrenic > control				
Frontal pole (10)	4.33	−2	62	−6
Left prefrontal cortex (47)	3.85	−50	30	−4
Left orbitalfrontal cortex (11)	3.66	−14	44	−20
Left prefrontal cortex (47)	3.20	52	48	−8
Between-group comparison: semantic > baseline				
Control > schizophrenic				
Right hippocampus	3.44	44	−22	−10
Left prefrontal cortex (47)	3.37	−38	32	−2
Schizophrenic > control				
Left orbitalfrontal cortex (11)	3.43	−10	40	−24
Frontal pole (10)	3.27	4	68	−14
Between-group comparison: 4× > 1×				
Control > schizophrenic				
No regions of statistical significance				
Schizophrenic > control				
No regions of statistical significance				
Between-group comparison: 4× > baseline				
Control > schizophrenic				
Right prefrontal cortex (47)	3.34	48	30	−2
Left prefrontal cortex (47)	3.22	−40	30	−8
Schizophrenic > control				
No regions of statistical significance				

we compared the accuracy of counting the correct number of T-junctions. Accuracy scores for the patients with schizophrenia (78 ± 16%) were not significantly different from those in control subjects (85 ± 18%) [$t(22) = 1.01$, $p = .32$]. We also examined the potential confounding effects of medication status on memory performance. Neither medication class [atypical vs. conventional: $t(10) = 0.98$, $p = .35$) nor anticholinergic status [positive vs. negative: $t(10) = 0.12$, $p = .9$] had an effect on overall recall accuracy.

PET Data

CONTROL SUBJECTS. In the control group, the use of a semantic encoding task (as compared with a perceptual task) during encoding resulted in greater retrieval-related regional cerebral blood flow (rCBF) in the right posterior hippocampus (Montreal Neurological Institute [MNI] coordinates: 26, −28, −6; $z = 3.49$) (Table 2). Word repetition during encoding resulted in greater rCBF during subsequent recall in the left anterior hippocampus (−32, −16, −16; $z = 3.44$). Similar hippocampal activation was observed when word retrieval after semantic and repeated encoding was compared with the active baseline task of lexical retrieval (right hippocampus: 30, −24, −8, $z = 4.06$; left hippocampus: −32, −18, −12, $z = 3.11$). In control subjects, therefore, the significant improvement in recall accuracy following each type of encoding manipulation was associated with hippocampal activation.

SCHIZOPHRENIA SUBJECTS. Unlike the control subjects, patients with schizophrenia did not demonstrate significant hippocampal activation during word retrieval after repeated or semantic encoding, even when statistical thresholds were extended down to $p < .05$, uncorrected. Instead, semantic encoding resulted in greater retrieval-associated rCBF in the left inferior frontal gyrus (Brodmann's area [BA] 47) and anterior medial prefrontal cortex (BA 10) (Table 2). Repetition of items during encoding led to greater rCBF in the right prefrontal cortex during memory retrieval (Table 2).

BETWEEN-GROUP ANALYSIS. Word-stem completion following semantic encoding was associated with greater retrieval-related rCBF increases in the right medial temporal lobe in the control subjects (28, −12, −6; $z = 3.64$) (Table 3). Similarly, greater hippocampal activity in control subjects was evident when word-stem completion following semantic encoding was compared with activity during the active baseline task (44, −22, −10; $z = 3.44$) (Table 3, Figure 2). Patients with schizophrenia, on the other hand, demonstrated greater activation than control subjects in the left and medial prefrontal cortex (Table 3).

There were no significant regions of differing activity during the retrieval of words that were encoded repeatedly as compared with those viewed only once. When compared with the active baseline condition, retrieval of repeatedly presented words was associated with greater bilateral activation of the dorsolateral prefrontal cortex in control subjects (Table 3). Analyses of both contrasts did reveal greater left hippocampal activation in the control subjects, but these were not significant at the predeter-

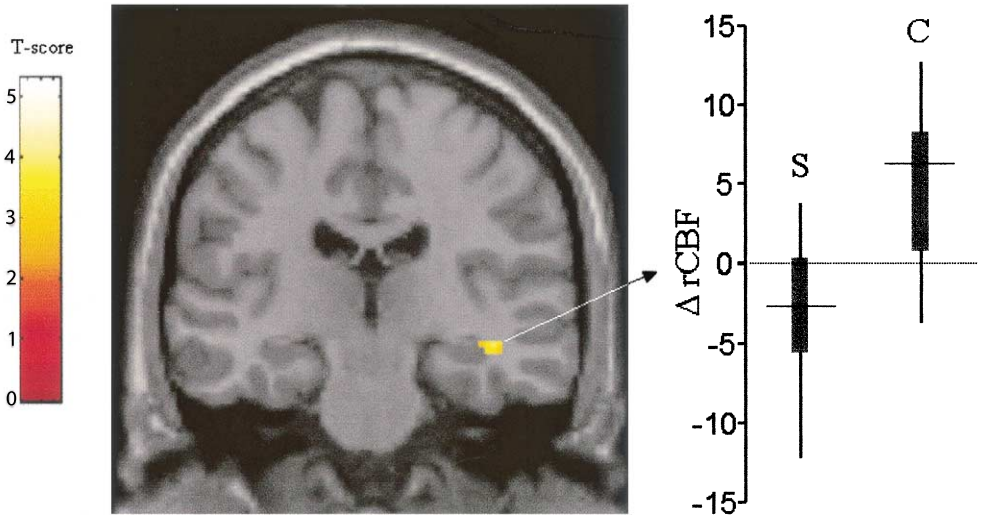

Figure 2. Greater modulation of blood flow in control subjects in the right hippocampus during recall after semantic encoding compared to active baseline. The region of significant activity ($p < .001$, uncorrected) is mapped onto a template structural magnetic resonance image of a single subject. The box plots indicate the mean, quartile distribution, and range of the change in right hippocampal regional cerebral blood flow (ΔrCBF) following semantic encoding versus active baseline. C = control, S = schizophrenia.

mined statistical threshold of $p < .001$ (4× vs. 1×: −34, −24, −6, $z = 2.63$; 4× vs. Baseline: −28, −20, −12, $z = 2.51$). No brain regions were significantly more active in schizophrenic subjects than in control subjects following item repetition at encoding.

To examine whether these between-groups differences were related to the medication status of the schizophrenia cohort, we ran simple regression analyses of the change in hippocampal blood flow versus chlorpromazine equivalents at the right (28, −12, −6) and left (−34, −24, −6) loci described above. At neither location was rCBF change correlated with medication burden (right hippocampus: df = 3, $r = .44$, $p = .56$; left hippocampus: df = 3, $r = .39$, $p = .61$). Similarly, using unpaired t tests, there was no difference in hippocampal modulation at these loci subjects on atypical versus conventional neuroleptics [right hippocampus: $t(10) = 0.50$, $p = .63$; left hippocampus: $t(10) = -0.63$, $p = .54$]. Finally, there was no difference in hippocampal modulation in these regions in patients on or off anticholinergic medications [right hippocampus: $t(10) = 0.45$, $p = .66$; left hippocampus: $t(10) = 0.07$, $p = .95$].

Discussion

Here we show that both item repetition and the use of a semantic encoding task were associated with memory retrieval–related hippocampal recruitment in control, but not schizophrenic participants. In the control group, the retrieval of repeatedly presented study items was associated with greater left anterior hippocampal activity, whereas the retrieval of items encoded via a semantic task was associated with recruitment of the right posterior hippocampus. Between-groups analyses indicated that both areas of activation were significantly greater in control than schizophrenic subjects, though only the right hippocampal region met *a priori* threshold criteria for statistical significance.

These findings replicate, in a completely novel cohort, our previous work highlighting the important role of the hippocampus in mediating depth of encoding effects on recall accuracy (Heckers et al 1998; Schacter et al 1996a, 1996b) and extend a growing literature indicating aberrant hippocampal/temporal lobe activity in patients with schizophrenia (Ganguli et al 1997; Hazlett et al 2000; Heckers et al 1998; Medoff et al 2001; Ragland et al 1998, 2001; Tamminga et al 1992). The novel experimental design of the current study also revealed that item repetition and the use of a semantic encoding task result in distinct patterns of greater retrieval-related hippocampal activity during subsequent word retrieval. Although we are cautious about implicating encoding-based interventions in the changes in blood flow measured at retrieval, it is of potential significance that abnormal hippocampal recruitment in schizophrenia appeared to be more substantial following semantic (as compared with perceptual) encoding. This finding suggests a disruption of the neural circuitry responsible for making meaningful associations between items in patients with schizophrenia.

Despite demonstrating impaired hippocampal recruitment during the retrieval of deeply encoded items, patients with schizophrenia nevertheless show a similar pattern of recall benefit across the various depth of encoding conditions. Although contrary to our initial hypothesis, which suggested that schizophrenic patients would not show intact modulation of memory performance, this finding is consistent with prior work indicating that patients with schizophrenia can benefit from encoding interventions to improve subsequent memory (Bauman 1971; Koh and Peterson 1978; Koh et al 1976). This intact ability to modulate performance via the use of simple encoding strategies may have important ramifications for clinical improvement of the cognitive deficits in schizophrenia. For example, repeated presentation of material, or encouraging the use of semantic (meaning-based) encoding of to-be-remembered items may lead to substantial improvement in cognitive performance and overall functioning. Indeed, similar arguments were recently put forth in a review of cognitive remediation for schizophrenia (Kurtz et al 2001). It is of further potential importance that this cohort was able to improve performance despite an overall lower estimated IQ than that of the control group. This suggests that such benefits are not limited to a "high-functioning" segment of the schizophrenia population.

It is intriguing that schizophrenic subjects were able to increase recall accuracy without the hippocampal recruitment seen in the control subjects. Two potential explanations seem most likely. First, the hippocampus is only one component of a cortical network subserving memory retrieval (Buckner and Koutstaal 1998; Fletcher et al 1997). Of particular interest have been the roles of the anterior and dorsolateral prefrontal cortices in memory retrieval, and the interaction of these areas with the medial temporal lobe system (Buckner and Wheeler 2001; Buckner et al 1998; Nolde et al 1998). Although not showing evidence of hippocampal recruitment, the patients with schizophrenia do show retrieval-related activation of the left ventral prefrontal cortex (BA 47) and anterior ventral prefrontal cortex (BA 10) during word retrieval following both methods of deep encoding. This region of left prefrontal cortex has been associated with greater depth of encoding in a number of studies, including both encoding and retrieval (Buckner et al 1999; Otten et al 2001; Ranganath et al 2000). These prefrontal regions may be engaged in a compensatory retrieval process in the schizophrenic subjects. Further work to better understand the relationship between memory-related activity of the hippocampus and prefrontal cortex in schizophrenia will be critical to evaluate such a mechanism.

A second explanation of the findings suggests that the hippocampal activation seen in control subjects is linked not only to the number of items remembered, but to *how* they are remembered. More specifically, in previous studies in healthy adults, words recollected following deep encoding are more likely to be "consciously" recollected (i.e., with awareness of the study episode and contextual details) rather than retrieved on the basis of simple familiarity or a "gut sense" (Gardiner 1988; Rajaram 1993). Indeed, these studies demonstrate that the superior recall of deeply processed items is due entirely to differences in conscious recollection (Blaxton and Theodore 1997). Importantly, recent work by Eldridge and colleagues demonstrates that retrieval-based hippocampal activation is due solely to the retrieval of items associated with conscious recollection (but is not related to familiarity-based recollection) (Eldridge et al 2000). The greater hippocampal activity during retrieval of deeply encoded items seen in the control group of the current study may similarly be related to this type of conscious recollection. Several studies have now demonstrated a deficiency of conscious recollection, with a tendency toward familiarity-based memory in patients with schizophrenia (Besche-Richard et al 1999; Danion and Rizzo 1998; Danion et al 1999; Heckers et al 1998; Huron et al 1995; Kazes et al 1999). The lack of hippocampal activation in schizophrenia could then be interpreted as impaired conscious recollection (Heckers et al 1998), whereas the ability to increase recall accuracy relies more on greater item familiarity. Although we did not record the "remember/know" judgments used to distinguish conscious from familiarity-based recollection (Tulving 1985), and therefore cannot examine this hypothesis using the current data, further evaluation of this intriguing explanation seems warranted.

As in our previous reports (Heckers et al 1998, 1999), the patients in this study were chronically ill male patients with a moderate degree of positive and negative symptoms. Given the relatively small sample size of this neuroimaging study, we felt it important to study a fairly homogeneous sample and therefore recruited all-male cohorts. This of course may limit the generalizability of our results: further examination of the nature of episodic memory in female patients with schizophrenia is needed to further evaluate the potential role of gender in mediating these effects.

All patients were taking neuroleptic medication, and four of the 12 were taking anticholinergic medication. Differences in memory performance or cerebral activation between these patients and the unmedicated healthy control group may therefore be confounded by this factor. Prior work on the impact of medication status on episodic memory has been mixed, though most recent studies report no significant effect (Goldberg and Weinberger 1996; Mortimer 1997) or even slight cognitive benefit, particu-

larly with atypical medications such as clozapine (Hagger et al 1993; Keefe et al 1999; Stip 1996). Indeed, withdrawal of neuroleptic medication may even adversely affect memory performance (Gilbertson and van Kammen 1997). Most (Berman et al 1986; Miller et al 1997; Ragland et al 2001), but not all (Medoff et al 2001), prior studies demonstrate no effect of medication status on prefrontal or medial temporal rCBF in schizophrenia. Concerns about this medication effect are somewhat assuaged by our analyses, which indicate no significant differences in memory performance or hippocampal rCBF modulation based on medication class (atypical vs. conventional antipsychotic) or the use of anticholinergic medication; however, a study of our word retrieval paradigm in a neuroleptic-naïve population would be necessary to rule out the potential confound of treatment with neuroleptic medication.

Patients with schizophrenia, although showing the performance benefits of deeper encoding, do not demonstrate the greater levels of hippocampal activity seen in control subjects. The inability to appropriately modulate hippocampal activity following deep encoding, particularly in relation to the use of a semantic encoding task, may be offset by greater activity in other regions known to be important for normal memory, including the anterior and dorsolateral prefrontal cortices. Alternatively, the lack of hippocampal modulation may reflect a qualitative, rather than quantitative, deficit in memory retrieval in patients with schizophrenia. The failure of hippocampal recruitment not withstanding, the fact that patients with schizophrenia were able to appropriately modulate performance following encoding intervention may have important implications for attempts at cognitive remediation in this population.

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References

Aleman A, Hijman R, de Haan EHF, Kahn RS (1999): Memory impairment in schizophrenia: A meta-analysis. *Am J Psychiatry* 156:1358–1366.

Bauman E (1971): Schizophrenic short-term memory: The role of organization at input. *J Consult Clin Psychol* 36:14–19.

Berman KF, Zec RF, Weinberger DR (1986): Physiologic dysfunction of dorsolateral prefrontal cortex in schizophrenia. *Arch Gen Psychiatry* 43:126–135.

Besche-Richard C, Passerieux C, Hardy-Bayle MC, Nicolas S, Laurent JP (1999): Fluency versus conscious recollection in category-production performance: The performance of schizophrenic patients. *Brain Cogn* 39:100–115.

Blair JR, Spreen O (1989): Predicting premorbid IQ: A revision of the National Adult Reading Test. *Clin Neuropsychol* 3:129–136.

Blaxton TA, Theodore WH (1997): The role of the temporal lobes in recognizing visuospatial materials: Remembering versus knowing. *Brain Cogn* 35:5–25.

Brebion G, Amador X, Smith MJ, Gorman JM (1997): Mechanisms underlying memory impairment in schizophrenia. *Psychol Med* 27:383–393.

Buckner RL, Kelley WM, Peterson SE (1999): Frontal cortex contributes to human memory formation. *Nat Neurosci* 2:311–314.

Buckner RL, Koutstaal W (1998): Functional neuroimaging studies of encoding, priming, and explicit memory retrieval. *Proc Natl Acad Sci U S A* 95:891–898.

Buckner RL, Koutstaal W, Schacter DL, Wagner AD, Rosen BR (1998): Functional-anatomic study of episodic retrieval using fMRI. I. Retrieval effort versus retrieval success. *Neuroimage* 7:151–162.

Buckner RL, Wheeler MA (2001): The cognitive neuroscience of remembering. *Nat Rev Neurosci* 2:624–634.

Chan AS, Kwok IC, Chiu H, Lam L, Pang A, Chow LY (2000): Memory and organizational strategies in chronic and acute schizophrenic patients. *Schizophr Res* 41:431–445.

Danion JM, Rizzo L (1998): Memory, consciousness and schizophrenia. *Schizophr Res* 29:46–46.

Danion JM, Rizzo L, Bruant A (1999): Functional mechanisms underlying impaired recognition memory and conscious awareness in patients with schizophrenia. *Arch Gen Psychiatry* 56:639–644.

Eldridge LL, Knowlton BJ, Furmanski CS, Bookheimer SY, Engel SA (2000): Remembering episodes: A selective role for the hippocampus during retrieval. *Nat Neurosci* 3:1149–1152.

First MB, Spitzer RL, Gibbon M, Williams JBW (1995): *Structured Clinical Interview for DSM-IV Axis I Disorders, Patient Edition (SCID-P), Version 2.* New York: New York State Psychiatric Institute, Biometrics Research.

Fletcher PC, Frith CD, Rugg MD (1997): The functional neuroanatomy of episodic memory. *Trends Neurosci* 20:213–218.

Ganguli R, Carter C, Mintun M, Brar J, Becker J, Sarma R, et al (1997): PET brain mapping study of auditory verbal supraspan memory versus visual fixation in schizophrenia. *Biol Psychiatry* 41:33–42.

Gardiner JM (1988): Functional aspects of recollective experience. *Mem Cognit* 16:309–313.

Gilbertson MW, van Kammen DP (1997): Recent and remote memory dissociation: Medication effects and hippocampal function in schizophrenia. *Biol Psychiatry* 42:585–595.

Goldberg TE, Weinberger DR (1996): Effects of neuroleptic medications on the cognition of patients with schizophrenia: A review of recent studies. *J Clin Psychiatry* 57:62–65.

Green MF (1996): What are the functional consequences of neurocognitive deficits in schizophrenia? *Am J Psychiatry* 153:321–330.

Green MF, Kern RS, Braff DL, Mintz J (2000): Neurocognitive deficits and functional outcome in schizophrenia: Are we measuring the "right stuff?" *Schizophr Bull* 26:119–136.

Hagger C, Buckley P, Kenny JT, Friedman L, Ubogy D, Meltzer HY (1993): Improvement in cognitive functions and psychiatric symptoms in treatment-refractory schizophrenic patients receiving clozapine. *Biol Psychiatry* 34:702–712.

Hazlett EA, Buchsbaum MS, Jeu LA, et al (2000): Hypofrontality in unmedicated schizophrenia patients studied with PET during performance of a serial verbal learning task. *Schizophr Res* 43:33–46.

Heckers S, Goff D, Schacter DL, Savage CR, Fischman AJ, Alpert NM, Rauch SL (1999): Functional imaging of memory retrieval in deficit vs. nondeficit schizophrenia. *Arch Gen Psychiatry* 56:1117–1123.

Heckers S, Rauch SL, Goff D, Savage CR, Schacter DL, Fischman AJ, Alpert NM (1998): Impaired recruitment of the hippocampus during conscious recollection in schizophrenia. *Nat Neurosci* 1:318–323.

Heckers S, Weiss AP, Alpert NM, Schacter DL (2002): Hippocampal and brain stem activation during word retrieval after repeated and semantic encoding. *Cereb Cortex* 12:900–907.

Huron C, Danion JM, Giacomoni F, Grange D, Robert P, Rizzo L (1995): Impairment of recognition memory with, but not without, conscious recollection in schizophrenia. *Am J Psychiatry* 152:1737–1742.

Kazes M, Berthet L, Danion JM, Amado I, Willard D, Robert P, Poirier MF (1999): Impairment of consciously controlled use of memory in schizophrenia. *Neuropsychology* 13:54–61.

Keefe RS, Bollini AM, Silva SG (1999): Do novel antipsychotics improve cognition? A report of a meta-analysis. *Psychiatric Ann* 29:623–629.

Koh SD, Kayton L, Peterson RA (1976): Affective encoding and subsequent remembering in schizophrenic young adults. *J Abnorm Psychol* 85:156–166.

Koh SD, Peterson RA (1978): Encoding orientation and the remembering of schizophrenic young adults. *J Abnorm Psychol* 87:303–313.

Kurtz MM, Moberg PJ, Gur RC, Gur RE (2001): Approaches to cognitive remediation of neuropsychological deficits in schizophrenia: A review and meta-analysis. *Neuropsychol Rev* 11:197–210.

Martin A (1999): Automatic activation of the medial temporal lobe during encoding: Lateralized influences of meaning and novelty. *Hippocampus* 9:62–70.

Medoff DR, Holcomb HH, Lahti AC, Tamminga CA (2001): Probing the human hippocampus using rCBF: Contrasts in schizophrenia. *Hippocampus* 11:543–550.

Miller DD, Rezai K, Alliger R, Andreasen NC (1997): The effect of anti-psychotic medication on relative cerebral blood perfusion in schizophrenia: Assessment with technetium-99 m hexamethylpropyleneamine oxime single photon emission computed tomography. *Biol Psychiatry* 41:550–559.

Mortimer AM (1997): Cognitive function in schizophrenia—do neuroleptics make a difference? *Pharmacol Biochem Behav* 56:789–95.

Nolde SF, Johnson MK, Raye CL (1998): The role of prefrontal cortex during tests of episodic memory. *Trends Cogn Sci* 2:399–406.

Otten LJ, Henson RNA, Rugg MD (2001): Depth of encoding processing effects on neural correlates of memory encoding: Relationship between findings from across- and within-task comparisons. *Brain* 124:399–412.

Ragland JD, Gur RC, Glahn DC, Censits DM, Smith RJ, Lazarev MG, et al (1998): Frontotemporal cerebral blood flow change during executive and declarative memory tasks in schizophrenia: A positron emission tomography study. *Neuropsychology* 12:399–413.

Ragland JD, Gur RC, Raz J, Schroeder L, Kohler CG, Smith RJ, et al (2001): Effect of schizophrenia on frontotemporal activity during word encoding and recognition: A PET cerebral blood flow study. *Am J Psychiatry* 158:1114–1125.

Rajaram S (1993): Remembering and knowing: Two means of access to the personal past. *Mem Cognit* 21:89–102.

Ranganath C, Johnson MK, D'Esposito M (2000): Left anterior prefrontal activation increases with demands to recall specific perceptual information. *J Neurosci* 20:U11–U15.

Schacter DL, Alpert NM, Savage CR, Rauch SL, Albert MS (1996a): Conscious recollection and the human hippocampal formation: Evidence from positron emission tomography. *Proc Natl Acad Sci U S A* 93:321–325.

Schacter DL, Savage CR, Alpert NM, Rauch SL, Albert MS (1996b): The role of hippocampus and frontal cortex in age-related memory changes: A PET study. *Neuroreport* 7:1165–1169.

Stip E (1996): Memory impairment in schizophrenia: Perspectives from psychopathology and pharmacotherapy. *Can J Psychiatry* 41:S27–S34.

Tamminga CA, Thaker GK, Buchanan R, Kirkpatrick B, Alphs LD, Chase TN, Carpenter WT (1992): Limbic system abnormalities identified in schizophrenia using positron emission tomography with fluorodeoxyglucose and neocortical alterations with deficit syndrome. *Arch Gen Psychiatry* 49:522–530.

Tulving E (1985): Memory and consciousness. *Can Psychol* 26:1–12.

Weiss AP, Heckers S (2001): Neuroimaging of declarative memory in schizophrenia. *Scand J Psychol* 42:239–250.