Fronto-Hippocampal Function During Temporal Context Monitoring in Schizophrenia

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Background: *Patients with schizophrenia have difficulty using contextual information to recall the source of information. Given the importance of the hippocampus and prefrontal cortex (PFC) in this type of memory, we hypothesized that this cognitive deficit stemmed from aberrant fronto-hippocampal activation during memory retrieval.*

Methods: *Patients with schizophrenia (n = 16) and age-matched comparison subjects (n = 16) underwent functional magnetic resonance imaging while performing a verbal memory task that requires intact use of temporal context. Blood oxygen-level dependent (BOLD) signal during correct memory decisions was compared between the two groups with statistical parametric mapping.*

Results: *Contrary to our hypotheses, patients with schizophrenia demonstrated nearly identical memory performance to that of the comparison subjects. Despite this, there were significant between-group BOLD signal differences, including a pattern of task-dependent hypofrontality or hyperfrontality. In addition, whereas the highest-performing subset of the comparison group demonstrated robust modulation of hippocampal activity, this pattern was not seen in the highest-performing patients with schizophrenia.*

Conclusions: *Despite memory performance similar to that of comparison subjects, patients with schizophrenia activated different neural pathways to achieve this success. This might reflect underlying neuropathology in fronto-hippocampal circuitry, the use of an alternate cognitive strategy to accomplish task performance, or both.*

Key Words: Schizophrenia, hippocampus, frontal lobe, memory, source monitoring, fMRI

Patients with schizophrenia demonstrate cognitive impairment in several domains, including verbal memory (Aleman et al 1999; Cirillo and Seidman 2003). These memory deficits present early in the course of illness, before the initiation of psychotropic medication, and are therefore considered a core component of this syndrome (Bilder et al 2000; Brewer et al 2005; Hoff et al 1999; Saykin et al 1994). Because memory performance is strongly correlated with functional outcome in the patient with schizophrenia (Milev et al 2005), there is considerable interest in developing new methods (both psychopharmacological [Friedman et al 1999] and psychotherapeutic [Wykes et al 2002]) to enhance memory. Understanding the psychological nature of these memory deficits and examining their neurophysiological underpinnings are therefore important preludes to better treatment.

Patients with schizophrenia tend to perform worse on tasks of explicit memory (conscious retrieval of specific information or events) than on tasks of implicit memory (procedural learning or priming) (Clare et al 1993; Danion et al 2001). Even within explicit memory patients seem to show greater deficits on tasks that require access to contextual information (where or when did I see this?), when compared with tasks requiring simple familiarity (did I see this?) (Danion et al 1999; Huron et al 1995). Prior work from our group showed this type of differential impairment, with a task designed to separate the influences of conscious recollection and familiarity on memory performance (Weiss et al 2002). In that study, participants were asked to distinguish previously studied words from novel words. The novel words were then repeated, after either a 2- or 24-word delay, equilibrating the degree of familiarity of these words with the words studied previously. The ability to correctly identify these repeated novel items as distinct from the initially studied items therefore required additional information, such as the temporal context in which the word was previously experienced. Patients with schizophrenia made more errors in assessing these repeating novel items, suggesting an impaired use of this type of contextual information.

In the present study we sought to examine the neural basis for this cognitive deficit by using functional magnetic resonance imaging (fMRI) to measure the change in blood oxygenation-level dependent (BOLD) signal during memory task performance. We were specifically interested in the change in cerebral activity that occurs when assessing the repeated items. Our focus was on the medial temporal lobe and prefrontal cortices, given the previously identified role of these structures in successful recollection of contextual information (Dobbins et al 2003; Kahn et al 2004) and the well-documented structural and functional abnormalities in these regions seen in patients with schizophrenia (Heckers 2001; Preston et al 2005; Ragland et al 2004; Seidman et al 1994). There were two primary hypotheses for this study: 1) relative to the comparison subjects, patients with schizophrenia would show a greater decline in accuracy from the initial to repeated presentation of novel items; and 2) successful identification of the repeating novel items would be associated with greater hippocampal and prefrontal BOLD signal than successful identification of the initially presented novel items, with this BOLD signal modulation being greater in the comparison group than in the patients with schizophrenia (i.e., a group × condition interaction).

Methods and Materials

Subjects

Seventeen outpatients (15 men and 2 women) with DSM-IV–defined schizophrenia (confirmed by the Structured Clinical Interview for DSM-IV [SCID]; First et al 1995) were recruited from

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Table 1. Characteristics of Schizophrenia and Comparison Subjects

	Schizophrenia $n = 16$		Comparison $n = 16$	
	Mean	SD	Mean	SD
Age (yrs)	46.9	8.3	46.8	6.5
Education (yrs)	13.0	1.9	14.3	2.5
Parental Education (yrs)[a]	13.0	1.9	12.5	2.7
Parental Socioeconomic Status[b]	3.2	1.3	2.7	1.3
Verbal IQ[c]	100.8	12.8	112.2	9.1
Duration of Illness (yrs)	22.0	9.4		
PANSS-Total	56.9	10.8		
Chlorpromazine Equivalents[d]	402	277		

PANSS, Positive and Negative Syndrome Scale.
[a]Data not available for one patient and one control.
[b]Hollingshead social strata: data not available for two patients and one comparison subject (1 = major business professional to 5 = unskilled laborer).
[c]Estimate based on North American Adult Reading Test (Blair and Spreen 1989); $p < .01$.
[d]Estimated with the Woods formulae for second generation antipsychotic drugs (Woods 2003).

our affiliated clinic in Boston. One male patient was excluded, owing to technical difficulties during scan acquisition. All patients were taking a stable dose of antipsychotic medication (14 taking second generation antipsychotic medications [7 taking clozapine, 5 taking olanzapine, 1 taking risperidone, and 1 taking aripiprazole] and 2 taking conventional antipsychotic medications [both taking prolixin decanoate]; mean chlorpromazine equivalents = 402 ± 277 mg/day; Woods 2003) and were not withdrawn from their medication for the purposes of the study. The current severity of illness was mild, on the basis of a mean total score of 57 ± 11 on the Positive and Negative Syndrome Scale (PANSS) (Kay et al 1992).

Sixteen age-matched subjects (14 men and 2 women), recruited by posted advertisement from the Boston area, served as a comparison group. Comparison subjects were free of any Axis I psychiatric condition (as determined by the SCID) and were not taking psychotropic medication. Neither patients nor comparison subjects had a history of major medical or neurological illness (e.g., seizure disorder, head trauma leading to altered mental state, or stroke). No subject met DSM-IV criteria for alcohol or other substance use disorder (excepting nicotine dependence) within the past 3 months.

There were no significant between-group differences in age, parental socioeconomic status, level of attained formal education, or mean parental education (Table 1). Comparison subjects did have a higher overall verbal IQ (112 ± 9 vs. 101 ± 13), as estimated by the North American Adult Reading Test (NAART) (Blair and Spreen 1989).

Before enrollment of subjects, the protocol was approved by the institutional review boards of both the Massachusetts General Hospital and the Commonwealth of Massachusetts Department of Mental Health. All participants provided written informed consent after a complete description of the study and administration of a brief questionnaire to ensure capacity to consent.

Procedure

The experimental paradigm was adapted from an old/new recognition memory test introduced by Underwood and Freund (1970) and modified by both Jennings and Jacoby (1997) and Dodson and Schacter (2002) (see also Fischler and Juola 1971; Koriat et al 1988). The stimuli consisted of 200 English words, divided into four 50-word lists for counterbalancing purposes. Each list was composed of 25 monosyllabic and 25 disyllabic words, and the lists were matched on word length (mean = 5, range = 3–8 letters), lexical frequency (mean = 52/million) (Kuchera and Francis 1967), printed familiarity (mean score = 551) (Coltheart 1981), and concreteness (mean score = 560) (Coltheart 1981). One hundred words (two randomly intermixed lists) were studied and were then seen as "old" items at test. The remaining 100 words served as "new" foils at test, with one-half of these items repeating after a 2-word delay and one-half after a 24-word delay. Four distinct counterbalances were created, with each list rotating through each of the four conditions (old, old, new2, and new24).

Stimuli were generated on a laptop computer with Presentation Version .76 (Neurobehavioral Systems, Albany, California). Words were rear-projected onto a hemi-circular tangent screen and viewed through a mirror mounted on the head coil of the MR scanner. While subjects were positioned in the scanner (but before scan acquisition), study words were presented for 3.25 sec (plus an interstimulus interval [ISI] of .25 sec) and subjects were asked to indicate the number of syllables in each word by button-press. Immediately after the study phase, participants were told that they would see "old" words (i.e., items seen during the syllable-counting phase) and "new" words (i.e., items not seen previously) and would be asked to distinguish between the two by pressing the appropriate button ("syllable counting phase" or "new"). While they were informed that items would repeat, they were told to focus on the "syllable-counting" versus "new" distinction, with specific instructions to continue to consider repeating new words as "new," because they were not encountered during the syllable-counting phase of the experiment. The 300 words (100 old, 100 new, 100 new-repeated) were then presented (duration of 3 sec, ISI of .5 sec) while fMRI data were collected.

Image Acquisition

Images were acquired on a Sonata 1.5 Tesla whole-body MRI scanner (Siemens AG, Munich, Germany), equipped for echo planar imaging (EPI). After automated scout and shimming procedures (to optimize field homogeneity), a high-resolution three-dimensional magnetization prepared rapid gradient echo (MPRAGE) sequence (1.2 mm slice thickness, repetition time [TR] = 2.5 sec, echo time [TE] = 3 msec, flip angle = 7°) was obtained. Functional MR images were acquired with a standard EPI sequence (TR = 2.5 sec, TE = 40 msec, flip angle = 90°, field of view = 200 × 200 mm^2, in-plane spatial resolution = 3.125 mm). During the functional run, 420 images were obtained at each of 25 interleaved oblique coronal slices (5 mm width) oriented perpendicular to the anterior commissure–posterior commissure line. To allow for longitudinal magnetization to reach equilibrium, the first four acquisitions were discarded.

Statistical Analysis

Behavioral Data. Statistical analysis of behavioral data was performed with SPSS version 11.0 (SPSS, Chicago). Group means for syllable counting accuracy, response accuracy for old items (hit rate), and the false characterization of new items as old during their initial presentation (false alarm rate) were compared with an unpaired Student *t* test. Old/new discrimination accuracy and response bias were calculated with the signal detection parameters of d' and C respectively, on the basis of the hit rate and false alarm rate of each subject (Macmillan and Creelman 1991). Because hit rates of 0 or 1 lead to undefined values in

these analyses, the data were transformed in standard fashion by adding .5 to each individual's hit total and dividing by $n + 1$ (rather than n) (Snodgrass and Corwin 1988).

To examine the effect of word repetition on accuracy, the response accuracy for new words (correct rejection rate, CR) was calculated at the initial presentation (CR_0), at the 2-word delay (CR_2), and at the 24-word delay (CR_{24}). Note that accuracy calculations for these repeated presentations included only those words correctly identified as new at the initial presentation. These correct rejection rates were then entered into a repeated measure analysis of variance (ANOVA), with group (comparison vs. schizophrenia) as a between-subject factor and delay (initial, 2, and 24) as within-subject factors.

For each subject, mean reaction times (RTs) were calculated for the correctly identified new items at each level of delay (i.e., CR_0, CR_2, and CR_{24}), with all RTs recorded within the 3.5-sec stimulus window. These means were then entered into a repeated measure ANOVA, with group as a between-subject factor and delay as a within-subject factor.

Functional Imaging Data. Functional imaging data were analyzed with statistical parametric mapping (SPM 99, Wellcome Department of Imaging Neuroscience, London, United Kingdom) running in Matlab5.3 (Mathworks, Natick, Massachusetts). Before statistical analysis, the data were processed in the following manner: images were slice-time corrected (to adjust for slice acquisition at different time points within the TR), realigned and resliced to correct for movement artifact, spatially normalized to the Montreal Neurological Institute (MNI) standard template (ICBM152) with a 12-parameter affine transform, and spatially smoothed with a three-dimensional 8 mm full-width half-maximum Gaussian filter to reduce spatial noise. The maximal degree of movement in either Cartesian coordinates (in millimeters) or rotational coordinates (in radians) did not differ significantly between the two groups (mean degree of maximal movement: Comparison: 1.57 ± .81 mm and .019 ± .026 radians; Schizophrenia: 2.14 ± .94 mm and .026 ± .027 radians; unpaired t tests: $p = .08$ and $p = .47$, respectively). A high-pass filter was then applied to the data to remove low-frequency drift in the signal.

The events of interest, as defined by subject response, were entered into a general linear model. Voxel-based analyses tested whether event-type (e.g., CR_0, CR_2, CR_{24}), modeled as a "boxcar" function convolved with the canonical hemodynamic response function and its temporal and dispersion derivatives, explained substantial variance components in the BOLD signal. To test the primary hypotheses, we performed within-subject contrasts to compare activity during the correct rejection of repeated new items with activity during the correct rejection of initially presented new items ($CR_2 > CR_0$ and $CR_{24} > CR_0$). To explore the possibility that subgroups of subjects (defined by memory accuracy) would demonstrate differential patterns of cerebral activation, we conducted post hoc analyses on the basis of a median split of the decrease in accuracy from CR_0 to CR_{24}. This allowed us to assess the change in cerebral activity in both high-performing subjects showing little effect of delay (mean decrease in accuracy of 3%) and those subjects who showed significant susceptibility to delay (mean decrease in accuracy of 34%). For all first-level contrasts, subjects with fewer than 12 trials of any event type were excluded from the analysis (two comparison subjects and two patients with schizophrenia). For the remaining subjects, comparison subjects had fewer trials than patients in the CR_0 event type (82 ± 12 vs.91 ± 5; $t = -2.46$, $p < .05$), but there were no between-group differences in the mean number of the other two event-types (CR_2: 36 ± 9 vs. 36 ± 8; CR_{24}: 28 ± 9 vs. 32 ± 8).

Within-subject contrast images were then entered into second-level t tests to examine both within-group and between-group effects. To disambiguate the direction of the observed results, between-group analyses were confined to only those regions showing significant main effects in the corresponding within-group contrast. Statistical parametric maps were thresholded at an uncorrected $\alpha < .001$ ($z \geq 3.09$), with a cluster extent threshold of three contiguous voxels. The localization of voxel maxima were confirmed by converting the SPM-generated MNI coordinates to Talairach coordinates (www.mrc-cbu.cam.ac.uk/Imaging/mnispace.html) and plotting these coordinates on the Talairach atlas (Talairach and Tournoux 1988) with a web-based database (Talairach Daemon, Research Imaging Center, San Antonio, Texas).

Results

Behavioral Data

Syllable counting accuracy did not differ between comparison subjects (mean ± SD: 97% ± 3%) and patients with schizophrenia (95% ± 7%) [$t(30) = 1.35$, $p = .19$]. The RTs for syllable counting were, however, significantly faster in the comparison subjects [907 ± 207 msec vs. 1298 ± 305 msec; $t(30) = -4.24$, $p < .0001$].

The two groups demonstrated similar overall memory performance, as assessed by d', a measure of old/new item discrimination [control: 1.07 ± .38 vs. schizophrenia: 1.25 ± .58; $t(30) = -1.02$, $p = .32$]. The two groups also demonstrated similar response tendencies, as assessed by C, a measure of response bias [control: .41 ± .38 vs. schizophrenia: .66 ± .51; $t(30) = -1.54$, $p = .13$].

As expected, accuracy of response to new items decreased with the length of repetition delay [ANOVA-main effect of delay: $F(2,60) = 18.26$, $p < .0001$] (Figure 1A). Both groups showed similar overall accuracy toward these new items [ANOVA-main effect of group: $F(1,30) = .31$, $p = .58$], and there was no evidence for a significant group × delay interaction [$F(2,60) = .70$, $p = .50$]. Thus, contrary to our initial hypothesis, patients with schizophrenia were as accurate as comparison subjects in categorizing these repeated new words. Both groups demonstrated substantial intersubject variability in the accuracy of their responses to repeating new words, with some subjects showing no diminution in accuracy and others showing a substantial decline (Figure 1B). A median split of the change in accuracy between CR_0 and CR_{24} was employed in post hoc fashion to divide each group into "high-performing" and "low-performing" subgroups (overall decline in accuracy of 3% and 34%, respectively). Despite this dramatic difference in performance over the delay, there were no significant differences in any of the measured demographic variables (including IQ) when compared between these two subgroups. Similarly, within the two schizophrenia subgroups, there were no significant differences in medication burden, duration of illness, or symptom profile as measured by the PANSS.

There was a trend toward increased RTs with greater length of repetition delay [ANOVA-main effect of delay: $F(2,60) = 2.46$, $p = .09$]. This pattern was similar in both groups, whereas there was no significant group × delay interaction [$F(2,60) = .82$, $p = .45$] nor was there an overall difference in RT [ANOVA-main effect of group: $F(1,30) = .35$, $p = .56$]. There was, however, a trend toward a difference between the high-performing and low-performing subgroups: the prolongation in RT from CR_0 to

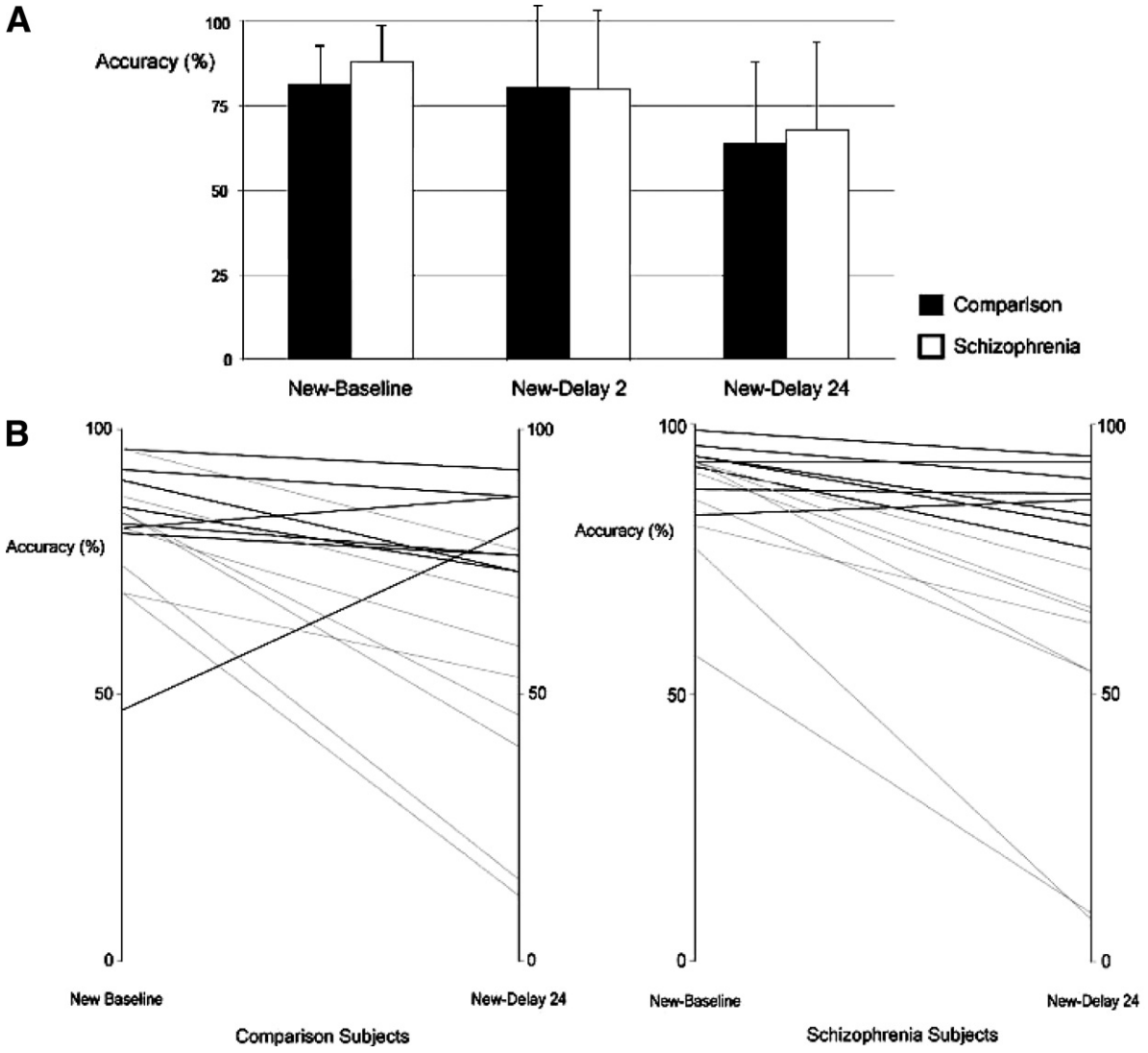

Figure 1. (A) Mean accuracy of response (± SD) to new items during their initial presentation and their repeated presentation after a 2- or 24-word delay. **(B)** Accuracy of response to new items during their initial presentation and their repeated presentation after a 24-word delay showing the intersubject variability of performance. With a median split of the change in accuracy across the condition, high-performing (delay resistant) subjects are represented by a dark line, low-performing (delay susceptible) subjects by a light line.

CR_{24} was only 9 msec in the former group and 147 msec in the latter [$t(30) = 1.77$, $p = .09$].

Functional Imaging Data

Prefrontal Activation. Despite nearly identical behavioral performance, there were significant between-group differences in the prefrontal BOLD signal pattern associated with a correct response to repeated items when compared with their initial presentation. After a two-word delay, comparison subjects showed increased activity in four discrete areas of the right prefrontal cortex, corresponding to Brodmann's areas 9 and 10 (Table 2). Patients with schizophrenia did not show statistically significant BOLD signal change within the prefrontal cortex in this contrast. Between-group comparisons confirmed this pattern of relative hypofrontality, because comparison subjects demonstrated two clusters of greater activation within the right prefrontal cortex.

This pattern was completely reversed after the 24-word delay. In this contrast comparison subjects failed to show significant prefrontal activation, whereas the patients with schizophrenia demonstrated significant BOLD signal increases in the frontal pole bilaterally (Brodmann area 10) and the right lateral prefrontal cortex (Brodmann area 45/47) (Table 3). These areas did not, however, show significant differential activation when between-group statistical comparisons were performed.

When the 24-word and 2-word delay conditions were compared directly, the patients with schizophrenia showed significant BOLD signal increase across the two conditions in four distinct areas of the prefrontal cortex bilaterally, a pattern not seen in comparison subjects (Table 4). In this contrast, the patients with schizophrenia now evinced a pattern of relative hyperfrontality, because three prefrontal clusters showed greater BOLD signal change in patients as compared with the control

Table 2. Cerebral Activity During Correct Identification of New Items After a Two-Word Delay (CR_2) Compared with Their Initial Presentation (CR_0)

	Comparison				Comparison > Schizophrenia				Schizophrenia				Schizophrenia > Comparison			
Cerebral Domain	X	Y	Z	*Z* Score	X	Y	Z	*Z* Score	X	Y	Z	*Z* Score	X	Y	Z	*Z* Score
Limbic-Paralimbic																
Anterior cingulate (32)	2	34	34	3.33												
Posterior cingulate (23/31)									−30	−60	22	3.27	−28	−60	20	3.61
Right insula (13)	38	18	8	3.30	34	20	10	3.50								
Heteromodal Cortices																
Right prefrontal (9)[a]	22	60	30	3.87	20	52	28	3.44								
Right prefrontal (9)[a]	40	44	28	3.65												
Right prefrontal (10)[a]	40	52	10	3.48	38	56	10	3.55								
Right prefrontal (10)[a]	22	56	4	3.45												
Precuneus (7/31)	4	−58	42	4.90												
Precuneus (7/31)	14	−58	32	4.38	14	−58	32	4.02								
Precuneus (7/31)	−4	−58	44	3.88												
Right parietal (39/40)	46	−54	22	4.29												
Right parietal (39/40)	52	−54	30	4.23	52	−54	34	3.43								
Left parietal (39/40)	−64	−46	28	3.61												
Left parietal (39/40)	−62	−56	16	3.54												
Left parietal (39/40)	−56	−50	14	3.35												
Unimodal Cortices																
Right inf. temporal (20)	52	−18	−14	4.24												
Right inf. temporal (20)	58	−28	−12	3.97												
Left inf. temporal (20)	−58	−30	−14	4.68												

Locations of those voxel maxima reaching the a priori statistical threshold ($p < .001, Z > 3.09$) in within- and between-group analyses are shown. Numbers listed in parentheses indicate approximate Brodmann areas.

[a]Areas of a priori interest (i.e., fronto-hippocampal areas).

cohort, most significantly in the left ventrolateral prefrontal cortex (Figure 2).

Hippocampal Activation. Neither comparison nor schizophrenia subjects demonstrated significant hippocampal BOLD signal change in any of the three planned contrasts (CR_2 vs. CR_0; CR_{24} vs. CR_0; CR_{24} vs. CR_2). Similarly, between-group comparisons did not indicate any statistically significant differences in hippocampal activation across these three event types.

Table 3. Cerebral Activity During Correct Identification of New Items After a 24-Word Delay (CR_{24}) Compared with Their Initial Presentation (CR_0)

	Comparison				Comparison > Schizophrenia				Schizophrenia				Schizophrenia > Comparison			
Cerebral Domain	X	Y	Z	*Z* Score	X	Y	Z	*Z* Score	X	Y	Z	*Z* Score	X	Y	Z	*Z* Score
Limbic-Paralimbic																
Anterior cingulate (33)	8	16	26	3.46												
Posterior cingulate (23/31)									−2	−36	40	3.27				
Left temporal pole (38)									−30	12	−30	3.81	−34	16	−38	3.32
Heteromodal Cortices																
Right prefrontal (10)[a]									26	52	0	4.36				
Left prefrontal (10)[a]									−24	62	2	3.76				
Right prefrontal (45/47)[a]									56	22	−6	3.51				
Right prefrontal (45/47)[a]									46	34	−16	3.42				
Precuneus (7/31)									−14	−50	40	3.26				
Medial parietal (5/7)	−10	−36	62	3.74					2	−34	62	3.62				
Unimodal Cortices																
Right inf. temporal (20)	52	−2	−20	3.50					52	2	−24	3.83	52	4	−26	3.29
Right inf. temporal (20)									64	−38	−8	3.79				
Motor																
Left cerebellum	−32	−54	−46	3.44	−34	−56	−46	3.51	−46	−60	−36	4.22				
Left putamen	−34	14	−6	3.49												
Left thalamus									−10	−2	12	3.49	−8	−4	12	3.33
Left SMA (6)									−6	−20	76	3.72				
Right SMA (6)									2	−12	58	3.33				

Locations of those voxel maxima reaching the a priori statistical threshold ($p < .001, Z > 3.09$) in within- and between-group analyses are shown. Numbers listed in parentheses indicate approximate Brodmann areas.

SMA, supplementary motor area.

[a]Areas of a priori interest (i.e., fronto-hippocampal areas).

Table 4. Cerebral Activity During Correct Identification of New Items After a 24-Word Delay (CR_{24}) Compared with Their Presentation After a 2-Word Delay (CR_2)

	Comparison				Comparison > Schizophrenia				Schizophrenia				Schizophrenia > Comparison			
Cerebral Domain	X	Y	Z	*Z* Score	X	Y	Z	*Z* Score	X	Y	Z	*Z* Score	X	Y	Z	*Z* Score
Limbic-Paralimbic																
Anterior cingulate (32)									2	18	46	3.81				
Right insula (13)									44	24	16	3.51	44	24	16	3.59
Left temporal pole (38)									−52	−4	−10	3.27				
Heteromodal Cortices																
Left prefrontal (46)[a]									−46	42	−12	4.35	−46	44	−10	4.14
Left prefrontal (47)[a]									−28	14	−24	3.74				
Right prefrontal (47)[a]									30	14	−22	3.14	32	12	−16	3.67
Right prefrontal (9)[a]									28	48	34	3.45	28	48	34	3.48
Precuneus (7/31)									12	−46	68	4.06				
Motor																
Left SMA (6)									−8	8	58	3.64	−6	16	54	3.68
Left SMA (6)									−6	−20	76	3.44				
Left cerebellum									−42	−62	−34	3.45	−42	−60	−34	4.18
Left caudate									−12	10	8	3.36	−10	8	6	3.47
Left caudate									−6	10	−6	3.29				

Locations of those voxel maxima reaching the a priori statistical threshold ($p < .001, Z > 3.09$) in within- and between-group analyses are shown. Numbers listed in parentheses indicate approximate Brodmann areas.

SMA, supplementary motor area.

[a]Areas of a priori interest (i.e., fronto-hippocampal areas).

The importance of the hippocampus became clearer when comparing the long-delay activation patterns between the high-performing and low-performing subgroups. When compared with the low-performing comparison subgroup, those comparison subjects who demonstrated little or no tendency to false alarm to delay items showed substantially greater activity in a single region: the left hippocampus (Figure 3). In fact, within the comparison group as a whole, the change in BOLD activity from CR_0 to CR_{24} within the left hippocampus showed a trend-level linear correlation with the change in accuracy between these two conditions (Pearson $\rho = .50$, $p = .07$). Thus, those comparison subjects who demonstrated the greatest hippocampal modulation were those who performed most accurately during the delay condition.

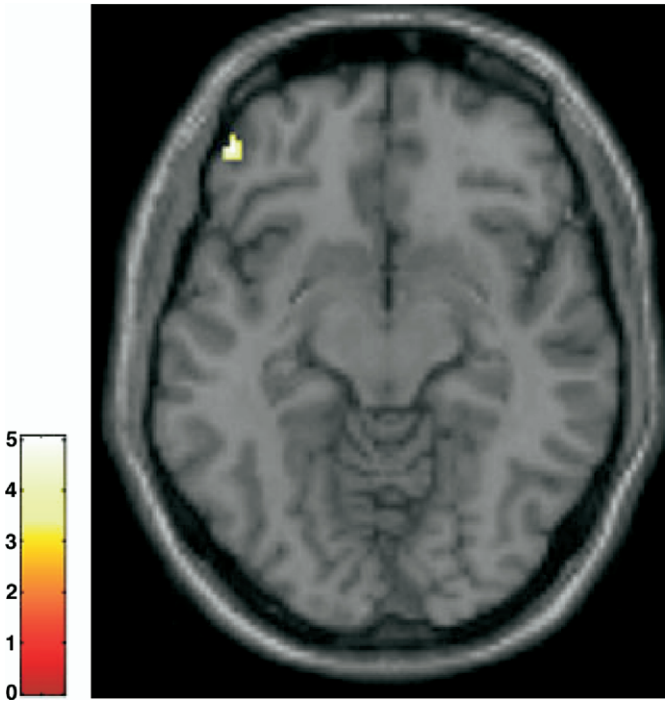

Figure 2. Hyperfrontality in patients with schizophrenia during long delay when compared with short delay. *T* statistic map displayed on a high-resolution template of the brain shows an area of significant between-group blood oxygenation level dependent (BOLD) signal difference (schizophrenia > comparison) in the left ventrolateral prefrontal cortex (-46/44/-10; $Z = 4.14$).

This correlation between medial temporal lobe modulation and accuracy was not seen in the patients with schizophrenia: of the areas showing significant activity in high-performing patients, none showed differentially greater activity when compared with low-performing patients. When the highest-performing comparison subjects were then contrasted with the highest-performing patients, one voxel (-32/-20/-14; $Z = 3.35$) within the left hippocampus was significantly greater in the former group, whereas modulation in the right motor cortex (30/-18/64; $Z = 3.96$) was significantly greater in the latter.

Activation Outside the Fronto-Hippocampal Network. Analyses across the entire brain revealed a number of additional between-group activation differences in regions not identified in our a priori hypotheses. After the two-word delay, comparison subjects complemented the pattern of prefrontal activation previously described with activation of network of areas known for their role in recollecting previously experienced visual information, including the lateral parietal cortices, precuneus, and right inferior temporal lobe (Table 2). Increased activity was also seen in the anterior cingulate cortex, perhaps related to the necessary suppression of the prepotent "old" response required to correctly label these repeating items as "new." In contrast, this condition led to increased activation in only a single area of the left posterior cingulate cortex in the patients with schizophrenia. Between-group analyses demonstrated that the precuneus and right parietal cortex were more active in the comparison group, whereas the posterior cingulate cluster was more active in the patient sample.

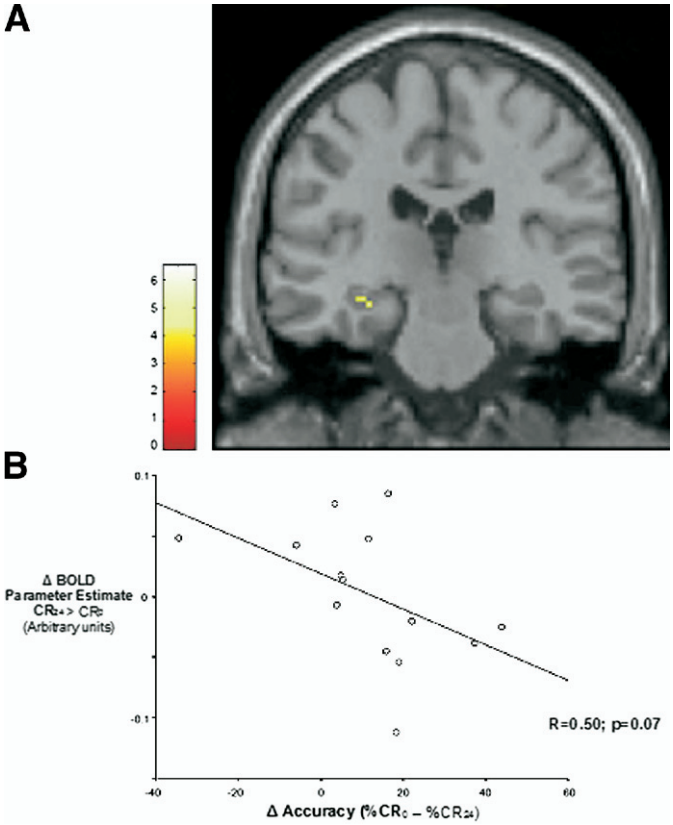

Figure 3. (A) Relationship between hippocampal activation and memory performance in comparison subjects. *T* statistic map displayed on a high-resolution template of the brain shows the single area of greater blood oxygenation level dependent (BOLD) signal change in high-performing (vs. low-performing) comparison subjects (left hippocampus; -30/-24/-12; $Z = 3.42$). **(B)** A scatterplot shows the linear relationship between change in hippocampal BOLD signal (as defined by the unitless statistical parametric mapping contrast parameter estimates) and change in accuracy (percent accuracy of response to initial minus delayed presentation of new item) for this region. CR_0, response accuracy for new words calculated at the initial presentation; CR_{24}, response accuracy for new words calculated at the 24-word delay.

After the 24-word delay, comparison subjects once again activated the medial parietal cortex, right inferior temporal lobe, and the anterior cingulate cortex (Table 3). Overall the patients with schizophrenia showed a similar pattern of activity, including BOLD signal increases in the medial parietal and right inferior temporal lobe (but not within the anterior cingulate cortex). Between-group analyses indicated greater left cerebellar activity in comparison subjects and greater activity in the left temporal pole, left thalamus, and right inferior temporal cortex in patients with schizophrenia.

When the 24-word and 2-word delay conditions were compared directly, patients showed a dramatic increase in cerebral activity with the longer delay, particularly in left-sided motor regions (Table 4). This pattern was not seen at all in the healthy control group, leading to a number of between-group differences—most significantly in the left cerebellum.

Discussion

Contrary to our a priori hypothesis, the patients with schizophrenia in this study did not demonstrate an impaired ability to identify repeating novel items. Despite nearly identical behavioral performance, however, there were significant differences in task-related cerebral activity, particularly within the prefrontal cortices. The results suggest that the neural path to successful memory performance might be different for patients with schizophrenia relative to the comparison group.

During the successful categorization of repeated novel items (as compared with their initial presentation) normal comparison subjects showed activation in medial and lateral parietal cortices, areas of the brain now known to signal the perceived "oldness" of information (see Wagner et al 2005 for recent review). This activity was accompanied by activation of the dorsal anterior cingulate cortex, a region implicated in motor control and response inhibition (Van Veen and Carter 2002). After the short delay (but not the long delay), comparison subjects also exhibited increased activity within the right prefrontal cortex, perhaps reflecting the use of recent contextual information (Braver and Barch 2002) or a judgment of temporal recency (Konishi et al 2002; Suzuki et al 2002; Zorrilla et al 1996) in making this memory decision. Thus, the cingulate and prefrontal activity seen in these subjects might facilitate correctly rejecting the item (by properly identifying it as "new") in the context of a parietal activity pattern that would otherwise signal an old item.

Unlike the comparison subjects, the patients with schizophrenia showed neither the parietal "old/new" activation nor the frontal lobe/anterior cingulate increases during the evaluation of new items repeated after a two-word delay. Indeed, there were minimal activation differences between the CR_2 and CR_0 conditions in this group. Thus, it seems that patients with schizophrenia evaluated the words repeated after a brief delay in the same manner as in the first presentation of these words, not using the recent contextual information that could aid in a memory decision. This finding is consistent with a number of recent studies demonstrating hypofrontality in patients with schizophrenia during on-line context processing, even when equilibrating for task performance (Barch et al 2001; Ford et al 2004; MacDonald et al 2005).

The pattern of activity in these patients after the longer delay was more consistent with that seen in the comparison group, with increased activity in unimodal visual areas and the medial parietal cortex/precuneus. During this condition, however, patients with schizophrenia now showed relatively greater prefrontal cortical activity than comparison subjects, with significant between-group effects seen in the right prefrontal cortex. The absence of anterior cingulate activity during this condition might have necessitated increased prefrontal activation, an area critical for post-retrieval monitoring (Achim and Lepage 2005). Alternatively, given that a longer delay between word pairs has been shown to place greater demand on temporal order judgments (Milner et al 1991), the hyperfrontality might represent an exaggerated response in the face of this challenge. The overall pattern of task-dependent hypofrontality and hyperfrontality in schizophrenia is intriguing, and as demonstrated by others, might reflect difficulty in modulating prefrontal activity to match cognitive demand (Fletcher et al 1998; MacDonald et al 2005; Manoach 2003; Quintana et al 2003).

With regard to the hippocampus, comparison subjects showed an interesting relationship between activity and behavioral performance. Those comparison subjects who were most capable of incorporating contextual information to make an accurate decision about repeated items were also the subjects who showed the greatest modulation of hippocampal activation. This pattern of hippocampal modulation was not seen in the patients with schizophrenia, even in those with superior memory perfor-

mance. These findings are in line with current theories regarding the normal role of the hippocampus in episodic memory broadly (Burgess et al 2002) and temporal context monitoring in particular (Howard et al 2005). They are also consistent with previous work from our lab and others demonstrating an impaired ability to modulate the activity of the hippocampus in relation to task demands in patients with schizophrenia, along with an increased compensatory activation of the prefrontal cortex (Heckers et al 1998, 1999; Ragland et al 2004; Weiss et al 2003). This impaired modulation might in fact stem from a condition of baseline hippocampal hyperactivity in the patients with schizophrenia (Medoff et al 2001), although this cannot be confirmed given the subtractive nature of fMRI analyses.

The patients with schizophrenia in the current study did not display a heightened degree of false recognition to the repeated presentation of novel items, suggesting an intact use of temporal context clues. This finding is in contrast to the results of our prior report (Weiss et al 2002) as well as behavioral studies from other groups describing impaired temporal order or recency judgments in patients with schizophrenia (Elvevag et al 2000; Rizzo et al 1996; Schwartz et al 1991; Waters et al 2004; but see Dreher et al 2001 and Rushe et al 1999 for other examples of intact memory for temporal order in schizophrenia). There are a number of potential explanations for this discrepancy. Methodological differences include subtle differences in the cognitive paradigms used (increased number of words, timed rather than self-paced) and the possible adverse effect of the MRI environment on cognitive performance (Raz et al 2005). Because these factors would likely accentuate between-group performance differences, they are unlikely to be playing a critical role. Although the sample size is in line with most current fMRI experiments of this nature, we cannot entirely exclude the possibility that we were underpowered to detect a difference in performance accuracy. We believe this is relatively unlikely. On the basis of the means and variances in our prior study, we selected a sample size (16/group) that would provide approximately 80% power (.78) to detect a 15% between-group difference in accuracy decline from baseline to 24-word delay, given a two-sided α of .05. Perhaps the most likely explanation relates to differences between the patient population capable of doing an "off-line" task with a laptop computer and those capable of performing the same task within the MRI scanner. When compared with the cohort of patients from the "word-only" arm from our prior experiment, the patients in the current study were slightly better educated [mean years of education: 13.0 vs. 11.8; $t(34) = 1.94$, $p = .06$] and were taking lower doses of antipsychotic medication [mean chlorpromazine equivalents: 403 vs. 627 mg/day; $t(32) = 2.16$, $p < .05$]. This type of selection bias, which is a relevant concern for all studies attempting to use fMRI in patient populations, might therefore limit our ability to generalize our findings to lower functioning patients with schizophrenia.

The generalizability of these results is further limited by the use of a predominantly male patient sample. Although the behavioral performance and hippocampal activation patterns of the four women in the study did not significantly differ from that seen in the male subjects, the study was not powered to examine gender differences in either domain. We also cannot rule out the possibility that medication with neuroleptic drugs might have contributed to the equilibration of behavioral performance, the between-group differences in cerebral activation, or both. As documented in a recent meta-analysis of the extant literature, atypical neuroleptic drugs seem to have a small but beneficial effect of long-term memory performance, although the benefits of clozapine seem to be less significant (Thornton et al 2006). The effect of treatment on neural physiology is less clear. A recent review of the 21 studies that have examined the longitudinal effects of antipsychotic medications on neurophysiological function found that normalization of cerebral activity is the most commonly seen pattern, although substantial methodological differences preclude confident conclusions at this time (Davis et al 2005). As shown by Snitz et al (2005), treatment with antipsychotic medication might normalize some aberrant patterns of activation (anterior cingulate cortex) while not affecting the hypoactivity seen elsewhere (dorsolateral prefrontal cortex). Overall, however, the strong similarity of our results to the work of Hofer et al (2003), who also found differential hypofrontality/hyperfrontality in the context of intact recognition memory in a cohort of unmedicated patients with schizophrenia, suggests that medication effects are not a sole explanation for our findings.

These results highlight two important considerations for future work in this area. First, the degree of variability in both behavioral performance and cerebral activation can no longer be ignored. Indeed, this variability might provide important clues regarding the mechanisms associated with healthy memory performance and its impairment in disorders like schizophrenia. We were unable to identify any demographic or illness-related characteristics that explained the tremendous differences between high- and low-performing subjects in this study. Given the recent work identifying specific genetic factors that contribute to both memory performance and task-related hippocampal activation (Egan et al 2003; Hariri et al 2003), it is tempting to speculate that these factors might have been at play here. Future work should consider the assessment of these factors. Second, the striking differences in cerebral activity, despite nearly identical group level performance, highlight the complex relationship between behavioral and imaging data (Shallice 2003; Wilkinson and Halligan 2004). Measuring behavioral data alone will not be able to identify these paths and might therefore be insensitive to the early effect of therapeutic interventions on cognition.

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