The Influence of Encoding Strategy on Episodic Memory and Cortical Activity in Schizophrenia

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Background: *Recent work suggests that episodic memory deficits in schizophrenia may be related to disturbances of encoding or retrieval. Schizophrenia patients appear to benefit from instruction in episodic memory strategies. We tested the hypothesis that providing effective encoding strategies to schizophrenia patients enhances encoding-related brain activity and recognition performance.*

Methods: *Seventeen schizophrenia patients and 26 healthy comparison subjects underwent functional magnetic resonance imaging scans while performing incidental encoding tasks of words and faces. Subjects were required to make either deep (abstract/concrete) or shallow (alphabetization) judgments for words and deep (gender) judgments for faces, followed by subsequent recognition tests.*

Results: *Schizophrenia and comparison subjects recognized significantly more words encoded deeply than shallowly, activated regions in inferior frontal cortex (Brodmann area 45/47) typically associated with deep and successful encoding of words, and showed greater left frontal activation for the processing of words compared with faces. However, during deep encoding and material-specific processing (words vs. faces), participants with schizophrenia activated regions not activated by control subjects, including several in prefrontal cortex.*

Conclusions: *Our findings suggest that a deficit in use of effective strategies influences episodic memory performance in schizophrenia and that abnormalities in functional brain activation persist even when such strategies are applied.*

Key Words: Episodic memory, fMRI, schizophrenia, strategy

Memory impairment in schizophrenia is a hallmark cognitive feature of the illness (Aleman et al 1999; for a review, see Kuperberg and Heckers 2000). One possible explanation for this impairment is that individuals with schizophrenia fail to use effective memory strategies. Strategic deficits have been reported in individuals with schizophrenia during tests of episodic memory (Brebion et al 1997; Gold et al 1992; Iddon et al 1998), as well as altered patterns of brain activation during both encoding and retrieval. Individuals with schizophrenia can benefit behaviorally when provided with effective encoding strategies, but the influence of such strategies on encoding-related brain activation has not been examined.

Episodic memory, the memory of unique events (Tulving 1983), is impaired in people with schizophrenia (Achim and Lepage 2003; Clare et al 1993; Danion et al 2001; Gold et al 1992; Rushe et al 1999; Toulopoulou et al 2003), but the mechanisms that lead to such impairment are unknown. One such mechanism may be that individuals with schizophrenia fail to generate effective mnemonic strategies when encoding and retrieving verbal information (Iddon et al 1998; Koh 1978; McClain 1983) or to encode verbal stimuli properly (Larsen and Fromholt 1976; Traupmann 1980). Interestingly, when provided with strategies that encourage deep semantic processing of stimuli, people with schizophrenia show improved subsequent memory (Koh and Peterson 1978; Ragland et al 2003), although it is not fully normalized.

The hypothesis that people with schizophrenia have deficits in the use of effective strategies in memory tasks is consistent with the presence of deficits in the function of the prefrontal cortex (PFC), particularly the dorsolateral PFC (Barch et al 2002; Fletcher et al 1998; Hofer et al 2003; Weinberger et al 1986). Patients with frontal lobe damage demonstrate planning difficulties (Shallice 1982) and show impaired use of organizational strategies (Gershberg and Shimamura 1995). Furthermore, impaired frontal lobe activity has been associated with impaired task performance in episodic memory paradigms (Barch et al 2002; Hazlett et al 2000; Heckers et al 1998; Ragland et al 2004; Weiss et al 2003). Deficits in frontal lobe activation in schizophrenia remain, however, even when memory performance is similar to control subjects (Crespo-Facorro et al 1999). These findings suggest that the application of memory strategies by people with schizophrenia are subserved by prefrontal regions (Nohara et al 2000; Ragland et al 2001, 2004), although altered hippocampal activity may also be involved (e.g., Barch et al 2002; Heckers et al 1998).

We previously found that individuals with schizophrenia show reduced activation of dorsolateral PFC during intentional encoding and retrieval of both words and faces (Barch et al 2002), as well as reduced functional laterality as a function of material type. Like control subjects, schizophrenia subjects showed greater activation of right ventrolateral PFC for faces than for words. Unlike control subjects, however, schizophrenia subjects did not show greater left ventrolateral PFC activation for words compared with faces. We hypothesized that these results reflect a failure to spontaneously use verbal processing strategies that would elicit enhanced activation for words in the prefrontal regions supporting such processes.

The levels-of-processing paradigm can be used to study the influence of strategy use on memory and brain activation. In this paradigm, participants are oriented to engage in either deep (i.e., abstract–concrete or living–nonliving judgments) or shallow (i.e., letter case or alphabetization judgments) processing of verbal stimuli, deep stimuli being associated with better recall and recognition (Craik and Lockhart 1972; Craik and Tulving 1975; for a recent review, see Craik 2002). Also, deep semantic processing at encoding preferentially activates areas in left PFC (Casasanto et al 2002; Fletcher et al 2003; Kapur et al 1994; Otten et al 2001; Otten and Rugg 2001).

Prior levels-of-processing studies in schizophrenia have shown that although people with schizophrenia show overall

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Table 1. Demographic and Clinical Data

Characteristic	Mean		Standard Deviation	
	Control Participants	Participants with Schizophrenia	Control Subjects	Participants with Schizophrenia
Age (years)	21.2	21.8	3.4	2.9
Sex (% male)	50	88.2		
Parents' Education (years)	15.2	15.3	2.1	2.8
Education (years)	13.8	11.9	2.6	2.0
Handedness (% right)	88.5	82.4		
Mean SAPS Global Item Score		2.4		1.4
Mean SANS Global Item Score		1.9		1.1
Poverty Symptoms		8.1		2.95
Disorganization		3.4		2.98
Reality Distortion		4.9		2.70
Atypical Medications Only (%)		82		
Combination Typical/Atypical (%)		12		
Anticholinergic Medication (%)		12		

SANS: Scale for the Assessment of Negative Symptoms; SAPS, Scale for the Assessment of Positive Symptoms.

worse memory performance compared with control subjects, they benefit from being oriented toward more effective encoding strategies (Heckers et al 1998; Koh and Peterson 1978; Ragland et al 2003; Weiss et al 2003). In addition, brain activation during memory retrieval differs as a function of encoding strategy (Heckers et al 1998; Weiss et al 2003). For example, impaired hippocampal activity relative to prefrontal activity occurs during memory retrieval (Heckers et al 1998; Weiss et al 2003). Such results suggest that people with schizophrenia experience deficits in explicit recollection that subsequently require greater retrieval effort, leading to enhanced prefrontal activity. These studies have not examined, however, whether at encoding people with schizophrenia engage the neural systems associated with deep encoding and enhanced subsequent memory, such as left PFC (Brodmann area [BA] 45/47; Baker et al 2001; Buckner et al 2001; Davachi et al 2001; Fletcher et al 2003; Kapur et al 1994; Otten et al 2001; Wagner et al 1998).

The goal of this study was to examine the influence of providing encoding strategies on brain activation and recognition performance in schizophrenia subjects. We used functional magnetic resonance imaging (fMRI) to examine brain activity while schizophrenia and control subjects performed incidental encoding of words and nonfamous faces. During scanning, participants were required to make semantic (deep) or orthographic (shallow) judgments for words and gender judgments for faces (intended to elicit deep processing) at encoding, followed by a yes–no recognition test. We predicted that participants with schizophrenia would benefit as much as control subjects from deep encoding and would activate similar regions of PFC during deep encoding (when task strategy is constrained). We also investigated the effect of the deep encoding manipulation on material-specific brain activity. We hypothesized that when the deep processing conditions for faces and words were compared (i.e., with specific strategies constrained), material type would produce laterality effects in PFC among individuals with schizophrenia.

Methods

Participants

Participants were 17 individuals with schizophrenia (15 male) and 26 healthy control subjects (13 male) who met diagnostic criteria from the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (American Psychological Association 1994). Subjects with schizophrenia were recruited to participate in studies of brain structure and function at the Conte Center for the Neuroscience of Mental Disorders at Washington University from a variety of outpatient treatment facilities. Control participants were recruited using local advertisements from the same community as the participants with schizophrenia. Exclusion criteria for control subjects included the presence of any lifetime history of Axis I psychiatric disorder or any first-degree relative with a psychotic disorder. Potential participants from either group were excluded for presence of any of the following: 1) meeting DSM-IV criteria for substance abuse or dependence within the past 3 months, 2) the presence of any clinically unstable or severe medical disorder, (c) head injury with documented neurologic sequelae or loss of consciousness, or (d) meeting DSM-IV criteria for mental retardation (mild or greater in severity). Demographic information is displayed in Table 1. Control and schizophrenia subjects were statistically similar on all demographic variables (p values $> .59$), with the exception of years of education ($t[41] = 2.51$, $p < .02$), for which control subjects were significantly higher than schizophrenia subjects.

All diagnoses were based on information derived from the Structured Clinical Interview for DSM-IV (SCID-IV; Spitzer et al 1990), which was conducted by a specially trained master's in social work–level research assistant who had access to hospital records and corroborative family sources. Additionally, an expert clinician conducted a semistructured interview and had access to all available medical records and collaborative sources but not to the SCID-IV interview results. A consensus meeting between the SCID-IV interviewer and the expert clinician determined the participant's final diagnosis.

Individuals with schizophrenia were assessed by specially trained research assistants using the Scale for the Assessment of Negative Symptoms (SANS; Andreasen 1983a) and the Scale for the Assessment of Positive Symptoms (SAPS; Andreasen 1983b), and the following scores were derived: Disorganization (global scores for positive thought disorder, bizarre behavior, and attention), Reality Distortion (hallucinations and delusions), and Negative Symptoms (alogia, blunted affect, anhedonia/asociality, and anergia/amotivation). Handedness was assessed using the

Edinburgh Handedness Inventory (Oldfield 1971). See Table 1 for means and standard deviations for symptom syndrome scores.

Written informed consent was obtained for all participants before participation in any aspect of the research. All experimental procedures were approved by the Institutional Review Board of Washington University in St. Louis and complied with these regulations.

Tasks and Materials

Subjects performed encoding and recognition tasks while being scanned. During the encoding tasks, stimuli (words or faces) appeared one at a time on the screen, and participants were required to engage in either deep (abstract/concrete judgments) or shallow ("Does the first or last letter of the word come first in the alphabet?") processing for words (in separate runs). A deep but not a shallow judgment was required for faces, because it has been difficult to achieve consistent levels-of-processing effects with faces. These tasks have been used previously in studies of deep versus shallow word processing (Demb et al 1995; Gold and Buckner 2002). During the recognition task, subjects indicated whether they had seen the current stimulus during the encoding phase of the experiment. The encoding tasks always took place before the recognition task for a particular stimulus type, but task order for words versus faces and for shallow versus deep word processing was counterbalanced across participants. Thus, subjects participated in five total scanning runs: shallow word encoding, deep word encoding, word recognition, deep face encoding, and face recognition.

Stimuli for the verbal tasks were visually presented words, 3–10 letters in length, presented in 48-point Geneva font. Stimuli for the nonverbal tasks were nonnameable faces, as previously reported (Barch et al 2002; Braver et al 2001; Kelley et al 1998; McDermott et al 1999).

Participants performed tasks in runs lasting 4.25 minutes (5 runs total). Each run included four task blocks of 16 trials each and three fixation blocks of 10 trials each interleaved in alternating order with the task blocks. Additionally, four fixation trials at the beginning were discarded in the analysis of the data (used to allow magnetic [MR] resonance signals to reach steady state), and there were four additional fixations at the end. Task blocks lasted 40 sec and fixation blocks lasted 25 sec. Each of the items in a task block was presented for 2 sec followed by a 500-msec interstimulus interval. During fixation blocks, a crosshair appeared continuously and participants were told to fixate. Visual stimuli were generated by an Apple PowerMac and PsyScope (Cohen et al 1993) and projected to participants with a Sharp LCD projector onto a screen positioned at the head end of the bore. Subjects viewed the screen through a mirror attached to the top of the MR head coil. A fiber-optic key press interfaced with the PsyScope Button box was used to record participant's behavioral performance.

Scanning

All scanning was performed on the 1.5-T Siemens VISION system. Functional images were collected using an asymmetric spin-echo echo-planar imaging (EPI) sequence sensitive to blood oxygenation level–dependent contrast (T2*) (TR = 2500 msec, TE = 50 msec, field of view = 24 cm, flip = 90°). During each functional run, 102 sets of axial images were acquired parallel to the anterior–posterior commissure plane (3.75 × 3.75mm in plane resolution), allowing complete brain coverage at high signal-to-noise ratio (Conturo et al 1996). Nineteen slices (7 mm thick) were acquired in each image. Structural images were acquired using a coronal MP-RAGE 3D T1-weighted sequence (TR = 9.7 msec, TE = 4 msec, flip = 10°; voxel size = 1 × 1 × 1.2 mm) and were used for between-subject registration (as described later) and anatomic localization.

Data Analysis

Functional magnetic resonance imaging preprocessing included the following: 1) compensation for slice-dependent time shifts, 2) elimination of odd–even slice intensity differences due to interpolated acquisition, 3) realignment of all data acquired in each subject within and across runs to compensate for rigid body motion (Ojemann et al 1997), 4) intensity normalization to a whole brain mode value of 1000, and 5) spatial smoothing with an 8-mm full-width-at-half-maximum Gaussian kernel. Functional data were transformed into the stereotaxic atlas space of Talairach and Tournoux (1988) by computing a sequence of affine transforms (first frame EPI to T2-weighted turbo spin echo (TSE) to MP-RAGE to atlas representative target) composed by matrix multiplication. All analyses described subsequently were conducted on the basis of atlas-transformed data resampled to 3 mm cubic voxels.

For each participant, we estimated the magnitude of task-related activation in each voxel using a general linear model (GLM) and a boxcar task function convolved with a Boynton hemodynamic response function, with separate estimates for each encoding task and material type (e.g., deep encoding—words, deep encoding—face, shallow encoding—words, shallow encoding—face). These estimates were then entered in appropriately designed analyses of variance (ANOVAs) and *t* tests (described in more detail later) that treated subjects as a random factor. To control for false-positive rates, we used a cluster-size threshold of nine contiguous voxels and a per-voxel alpha of at least .0004, corresponding to a corrected whole brain false positive rate of approximately .05. We required multiple effects to be significant simultaneously, a *p* value threshold of .02 being required for each effect, resulting in a combined significance of either .0004 (.02 * .02) or .000008 (.02 * .02 * .02; Barch et al 2001).

We examined group differences for brain regions sensitive to the levels-of-processing manipulation and brain regions that showed material sensitive effects during deep encoding. To identify task-responsive regions for the levels-of-processing effect, we required voxels to show all of the following effects: 1) significant task-related activation for either deep or shallow encoding tasks for either the control or schizophrenia group, using voxel-wise dependent sample *t* tests; 2) greater task-related activity for either deep encoding compared with shallow or for shallow encoding compared with deep, in either the control or schizophrenia group (or both), using voxelwise within-subject *t* tests; and 3) significant group differences in encoding task-related activation, using voxelwise ANOVAs with group (control, schizophrenic) as a between-subject factor and encoding depth (deep vs. shallow) as a within-subject factor (i.e., a group × encoding depth interaction). A similar procedure was used to identify regions showing group differences in material-sensitive brain regions: 1) greater activity in task compared with fixation during either deep encoding for words or faces in either control subjects or patients; 2) greater task-related activity for either words compared with faces or faces compared with words, using voxelwise within-subjects *t* tests; and 3) significant group differences in material sensitive activation (i.e., a group × material type interaction).

Table 2. Behavioral Data: Encoding and Recognition of Words and Faces, Mean (SD)

Task	Measure	Control Subjects	Participants with Schizophrenia
Word Encoding (Deep)	Accuracy	.81 (.08)	.73 (.10)[a]
	Reaction time (msec)	988 (188)	1139 (209)
Word Encoding (Shallow)	Accuracy	.93 (.04)	.87 (.04)[a]
	Reaction time (msec)	1071 (195)	1128 (195)
Word Recognition (New)	% Correct rejections	.81 (.12)	.79 (.23)
	Reaction time (msec)	1054 (143)	1158 (264)
Word Recognition (Deep)	% Hits	.87 (.13)	.78 (.22)
	Reaction time (msec)	945 (238)	1057 (218)
Word Recognition (Shallow)	% Hits	.64 (.23)	.56 (.23)
	Reaction time (msec)	1022 (288)	1051 (365)
Face Encoding (Deep)	Accuracy	.99 (.01)	.98 (.03)
	Reaction time (msec)	745 (154)	733 (113)
Face Recognition (New)	% Correct rejections	.76 (.09)	.67 (.12)[b]
	Reaction time (msec)	1119 (148)	1079 (150)
Face Recognition (Deep)	% hits	.66 (.20)	.50 (.22)[b]
	Reaction time (msec)	1099 (160)	1109 (249)

[a]Control > Schizophrenia, $p < .01$.
[b]Control > Schizophrenia, $p < .001$.

Behavioral Data

Accuracy and mean reaction times (RTs) for correct responses were examined separately for the incidental encoding tasks and the subsequent recognition tasks. Subsequent recognition responses were classified as "hits" if subjects correctly identified previously seen words. Recognition responses were classified as "correct rejections" when subjects correctly identified new words. The accuracy and RT data from the encoding and the recognition tasks were analyzed using ANOVAs and *t* tests.

Results

Behavioral Data: Words

Encoding Performance. The encoding data (accuracy and RT) were analyzed using repeated-measures ANOVAs with group (control, schizophrenic) as the between-subjects factor and depth (deep, shallow) as the within-subjects factor (see Table 2). The encoding accuracy ANOVA revealed a significant main effect of task type [$F(1,41) = 60.27$, $p < .001$] and a significant main effect of group [$F(1,41) = 16.85$, $p < .001$), with no significant task type × group interaction ($p > .46$). Post hoc comparisons revealed significantly better performance on the shallow (alphabetical judgments) than the deep task (abstract/concrete judgments) within each group ($p < .001$). Additional post hoc comparisons showed that control subjects performed significantly better than schizophrenia subjects on both the shallow and deep encoding tasks (both p values $< .008$).

For encoding RTs, there was no significant main effect of task type ($p > .12$), but there was a trend-level main effect of group [$F(1,41) = 3.467$, $p = .07$] and a significant task type × group interaction [$F(1,41) = 4.062$, $p = .05$]. Post hoc comparisons revealed significantly longer RTs for the schizophrenia group compared with control subjects during abstract/concrete judgments ($p < .02$) but not alphabetical judgments ($p > .34$).

Recognition Task Performance. The data from the recognition task (both accuracy and RT) were analyzed using a 2 × 2 ANOVA, with group (control, schizophrenic) as the between-subjects factor and depth (deep encoding, shallow encoding) as the within-subjects factor (see Table 2). There was a significant effect of depth [$F(1,41) = 44.9$, $p < .001$] and a trend-level effect of group [$F(1,41) = 3.41$. $p = .072$], but no significant depth × group interaction ($F < 1$). Overall, patients with schizophrenia were less accurate then control subjects in recognition, although only at a trend level. Patients and control subjects showed the same degree of benefit from the levels-of-processing manipulation, however. The control subjects were 23% more accurate for words encoded during the deep compared with the shallow condition, and the patients were 22% more accurate.

Behavioral Data: Faces

Face encoding performance was analyzed using a between-subjects *t* test (see Table 2). Control subjects ($M = .994$) performed the gender identification task significantly more accurately [$t(41) = 2.87$, $p < .001$] than individuals with schizophrenia ($M = .977$).

On the face recognition task, control subjects ($M = .41$) had significantly higher corrected hit rates for subsequent recognition of faces [$t(41) = 3.73$, $p < .01$] compared with participants with schizophrenia ($M = .17$).

Neuroimaging Data: Levels-of-Processing Effects

Our first goal was to identify brain areas with significantly more activity during deep than shallow encoding in each group, using voxel-wise ANOVAs with condition (task, fixation) and encoding task (deep, shallow) as within-subject factors. As shown in Table 3, 10 regions showed significant levels-of-processing effects; for example, left frontal cortical regions, including left inferior frontal (BA 45), middle frontal (BA 6), and superior frontal (BA 6) gyrus. In individuals with schizophrenia, there were also 10 regions that showed significant levels-of-processing effects (Table 3); for example, left (BA 45/47) and right (BA 45) inferior frontal gyrus, as well as left medial frontal gyrus (BA 46). Thus, both groups showed levels-of-processing effects in cortical regions typically active during deep semantic encoding (see Figure 1).

We next identified regions showing group differences for levels-of-processing effects. This analysis revealed three regions: left inferior frontal (BA 45), right inferior frontal (BA 45), and left middle frontal (BA 10) gyrus (see Figure 1). In all three of these regions, schizophrenia subjects showed significantly greater task-related activity for deep compared with shallow encoding (all ps $< .02$) than control subjects, who showed no significant

Table 3. Levels-of-Processing Effects (Deep vs. Shallow Encoding)

Region of Interest	Brodmann Area(s)	X	Y	Z	ROI *F* Value for Main Effect of Depth	Effect Size
Control Participants						
Left inferior frontal gyrus	45	−47	22	11	28.21	1.47
Left superior frontal gyrus	6	−13	13	62	20.21	1.25
Left middle frontal gyrus	6	−39	5	54	13.53	1.02
Right cerebellum		17	−31	−40	12.79	.99
Left middle temporal gyrus	39	−62	−55	13	12.00	.96
Right middle frontal gyrus	6	5	2	56	11.04	.92
Left inferior frontal gyrus	47	−48	33	−14	11.04	.94
Left precentral gyrus	6	−53	−5	27	8.35	.80
Left medial frontal gyrus	8	−45	18	43	7.45	.76
Left medial frontal gyrus	9	−38	38	31	7.22	.75
Participants with Schizophrenia						
Left inferior frontal gyrus	47	−50	16	−8	28.03	1.81
Left inferior frontal gyrus	47	−43	34	−4	25.31	1.73
Left inferior frontal gyrus	45	−48	22	8	17.23	1.42
Left medial frontal gyrus	46	−52	23	23	15.14	1.33
Right inferior frontal gyrus	45	43	20	0	12.66	1.22
Left inferior frontal gyrus	44	−48	7	28	9.19	1.08
Left inferior frontal gyrus	47	−34	15	−3	9.03	1.06
Left superior frontal gyrus	8	−6	30	48	8.98	1.03
Left middle frontal gyrus	46	−44	40	17	7.87	.96
Left middle frontal gyrus	10	−30	47	13	7.52	.94

ROI, region of interest.

differences for deep versus shallow ($ps > .31$). Also, schizophrenia subjects demonstrated significantly greater deep encoding related activation than control subjects in all three regions ($ps < .03$), but the groups did not differ in the degree of shallow encoding related activation in any of the three regions. These results suggest that schizophrenia subjects recruited regions typically associated with deep processing when oriented to a semantic processing strategy but also regions not typically engaged by control subjects in this paradigm. Although control subjects demonstrated significant task-related activity (task > fixation) in two of these regions (left and right BA 45) during deep verbal encoding, they did not show significantly greater activity for deep compared with shallow encoding in these two regions. We note, however, that there was another adjacent region of left BA 45 that showed significantly greater deep than shallow encoding related activity in both control subjects and individuals with schizophrenia.

Control participants performed significantly better on the encoding tasks than did participants with schizophrenia. To investigate possible performance effects on encoding-related brain activity, we selected a subgroup of eight schizophrenia subjects (matched on demographic variables and medication status) with mean deep encoding performance equal to that of the control group (81.4%) and compared brain activation in this subgroup of patients to control subjects in the three brain regions identified as showing group differences in levels of processing. In this analysis, only the left inferior frontal gyrus continued to show a group by depth by condition interaction, whereas the left BA 10 and right BA 45 regions no longer showed significant group differences in levels of processing. This result suggests that better performing patients do not show enhanced deep encoding related activity in L BA 10 or R BA 45. An alternative interpretation is that these nonsignificant effects simply reflect low power because the sample size for high performing patients ($n = 8$) is smaller than the total sample ($n = 17$). Examination of the effect sizes for these different regions does not support a low power interpretation, however, because the eta-squared values for the left BA 10 and right BA 45 regions in the high-performing group comparison were much smaller (.06 and .07) than the values for these same regions in the total sample (.22 and .16).

Neuroimaging Data: Material Specificity Effects

To test the hypothesis that people with schizophrenia fail to apply verbal processing strategies properly (Iddon et al 1998; Koh 1978), we first identified brain regions that showed material-sensitive activation (words > faces or faces > words) during the deep encoding conditions within each group, using voxelwise ANOVA with condition (task, fixation) and material (word, face) as within-subject factors. Control subjects (see Figure 2) demonstrated greater task-related activity for words than faces in left inferior and middle frontal cortex (BA 47), left temporal cortex, and left parietal cortex, among other areas. Control subjects demonstrated greater task-related activity for faces than words in right middle occipital gyrus (BA 19), right temporal and parietal cortices (BA 1), and left cerebellum. Subjects with schizophrenia, however, demonstrated greater task-related activity for words than faces in left PFC and temporal cortex, as well as in a number of other regions. Finally, individuals with schizophrenia demonstrated greater task-related activity for faces than words in many of the same regions as control subjects, including right middle temporal gyrus (BA 37), right hippocampus, and left cerebellum (see Figure 2).

We next identified 19 regions that showed group differences for material-sensitive effects (see Methods for description of how such regions were identified). As shown in Table 4, six of these regions were ones in which control subjects showed stronger material-sensitive effects than patients, including one region in left inferior PFC that was more active for words than faces in control subjects but not patients. As shown in Table 5, the remaining 13 regions were ones in which the individuals with

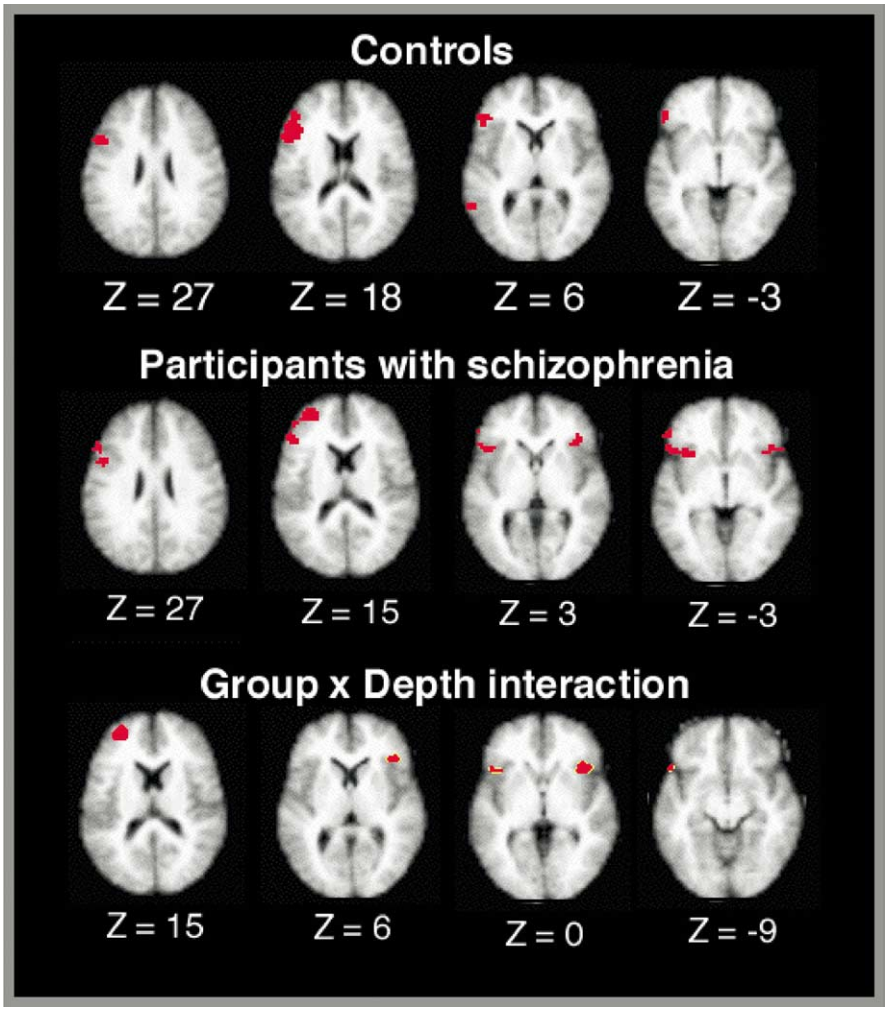

Figure 1. Levels-of-processing effects, in control participants (top), participants with schizophrenia (middle), and the group × depth interaction (bottom). Shown are regions of greater deep than shallow encoding-related activity. Active regions are shown in red. Regions of significant activity for control participants include left inferior frontal (Brodmann's area [BA] 45), left middle frontal (BA 6), and left superior frontal (BA 6) gyrus. Regions of significant activity for participants with schizophrenia include left inferior frontal (BA 45), right inferior frontal (BA 45), and left medial frontal (BA 46) gyrus. The three regions of significant between-group differences in levels-of-processing effects (deep encoding > shallow encoding) were left inferior frontal (BA 45; –46, 7, –9), right inferior frontal (BA 45; 45, 21, 4), and left middle frontal (BA 10; -37, 43, 20) gyrus, all of which were activated to a significantly greater degree in participants with schizophrenia compared with control participants.

schizophrenia showed greater material-sensitive effects than control subjects. Of the 13 regions, 12 were ones in which patients showed greater activity for words than faces, and many were in right PFC.

Discussion

The primary goal of this study was to determine the extent to which provision of encoding strategies would elicit cortical activity in brain areas typically associated with deep encoding in people with schizophrenia and improve recognition performance. Both the behavioral and neuroimaging results revealed typical levels-of-processing effects in participants with schizophrenia. As predicted, participants with schizophrenia showed significant recognition memory performance benefits for words encoded using deep encoding compared with shallow encoding. Such evidence is in agreement with previous findings (Chan et al 2000; Gold et al 1992; Koh and Peterson 1978) and contributes to the growing literature suggesting that people with schizophrenia can profit from mnemonic encoding strategies. Such strategies, however, were not able to equate fully the performance of the schizophrenia participants with that of the control subjects because the former still recognized fewer words. One possible explanation for this may relate to the nature of the recognition task we used, in which strategy was unconstrained. If the strategic use of memory cues can aid performance at recognition as well as encoding, and if patients did not spontaneously use such strategies at recognition, even the provision of beneficial encoding strategies would not normalize performance. Future studies could determine whether strategic instruction at retrieval as well as encoding could normalize performance of people with schizophrenia.

The neuroimaging data also suggest that participants with schizophrenia activate brain regions typically associated with deep semantic encoding, including the left inferior and middle frontal gyrus (Fletcher et al 2003; Kapur et al 1994; Otten et al 2001). Thus, when oriented toward proper encoding strategies, individuals with schizophrenia activate the same regions of PFC shown to be crucial to deep encoding processes in healthy control subjects (Buckner et al 2001; Wagner et al 1998). We also identified three regions (left inferior frontal [BA 45], right inferior frontal [BA 45], and left middle frontal gyrus [BA 10]), however, in which schizophrenia, but not control, subjects showed statistically greater deep than shallow encoding-related activity. This result is not predicted by the large body of literature regarding PFC hypoactivation in people with schizophrenia (Andreasen et al 1996; Barch et al 2002; Weinberger et al 1986). Greater PFC activity has been reported in schizophrenia compared with control subjects, however, during retrieval (Heckers et al 1998; Weiss et al 2003). In addition, a number of recent working memory studies have found increased PFC activity among patients, which has also been interpreted as a need to expend greater effort to remember the same or even a smaller amount of

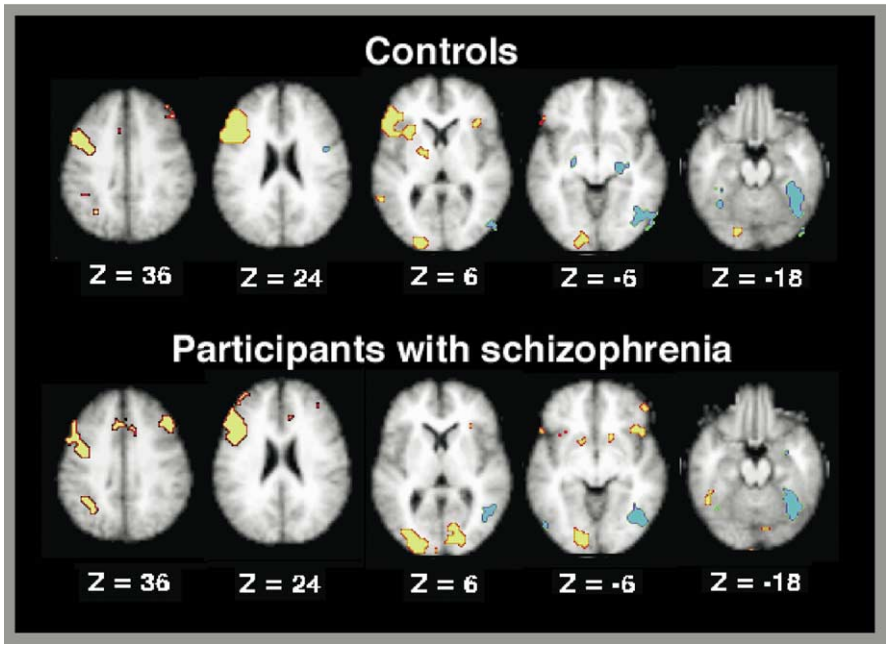

Figure 2. Material specificity effects (words vs. faces) during deep encoding in control participants (top) and participants with schizophrenia (bottom). Regions of significant word > face activity are shown in yellow, regions of significant face > word activity are shown in blue. Control participants show typical material-specific lateralization, with word-related activity left-lateralized and face-related activity right-lateralized. Participants with schizophrenia show a much more bilateral pattern of activity for deep encoding of words, but a similarly right-lateralized pattern of activity for deep face encoding.

information than control subjects (Callicott et al 2000). Thus, our results suggest that people with schizophrenia recruit additional regions of PFC to accomplish the same semantic processing strategies normally supported by a smaller subset of left prefrontal regions among healthy control subjects.

A second goal was to test the hypothesis that strategic constraint at the time of encoding could normalize material-specific brain activity, given our previous findings of a reduction in the normal left-lateralized prefrontal activation for verbal materials among individuals with schizophrenia. Consistent with this hypothesis, both patients and control subjects showed greater activation for words compared with faces in a number of left PFC regions, as well as left temporal and parietal regions. Thus, when oriented toward appropriate verbal processing strategies, the schizophrenia patients engaged many brain regions typically associated with verbal processing. However, they also showed greater activity in regions of right PFC for words compared with faces, possibly related to the nature of the deep encoding face task. Future studies should attempt to identify a more effective deep encoding task for faces.

These findings suggest that patients with schizophrenia activate the same verbal processing regions as control subjects when oriented toward an appropriate strategy, but they also activate a number of additional regions not engaged by control subjects, particularly in the right hemisphere. One interpretation is that the more widespread and bilateral frontal activity in schizophrenia is a means of compensating for impaired prefrontal function, as has been suggested to occur in elderly individuals (Buckner 2004; Cabeza et al 2002). Under this interpretation, there should be more activation in better performing subjects. Another interpretation of our findings is that the overrecruitment seen in schizophrenia is a manifestation of underlying pathology in PFC (and potentially other regions) and does not benefit performance. Under the pathology interpretation, there should be less extensive cortical activity in higher than lower performing patients because high performers presumably have less pathology than low performers. When examining a subgroup of patients that was matched to control subjects on deep encoding task performance, only one of the three regions (left inferior frontal gyrus) continued to show greater task-related activation in patients than control subjects. Furthermore, post hoc comparisons of the control group and a high-performing patient subgroup (M = 83.1%) and a low-performing subgroup eight 8 patients with schizophrenia (M = 66.1%) using the deep > shallow contrast revealed that in all three regions of interest (left inferior frontal, right inferior frontal, left middle frontal), the effect size for the deep > shallow contrast was greater in the low- than in the high-performing group (.90 vs. .44; .98 vs. .80; .86 vs. .66). These findings suggest that people with schizophrenia who perform worse on the encoding tasks recruit more extensive and bilateral

Table 4. Regions Showing Larger Material-Sensitive Effects in Control Subjects Than in Patients with Schizophrenia

Region of Interest	Brodmann Area(s)	X	Y	Z	ROI F-value for group × material type interaction	Effect size of material type: Control participants	Effect size of material type: Participants with Schizophrenia
Word > Face in Control Subjects							
Left interior frontal gyrus	45	−39	26	3	8.66	1.2473	.1615
Face > Word in Controls Subjects							
Left hippocampal gyrus	36	−27	−26	−16	12.42	1.2467	.4848
Left fusiform gyrus	37	−40	−42	−18	11.79	1.2366	.1833
Right postcentral gyrus	2	35	−33	63	11.76	1.2113	.3869
Right superior temporal gyrus	38	28	8	−37	9.39	.8818	.4650
Left cerebellum		−25	−39	−37	6.81	1.0031	.0145

Table 5. Regions Showing Larger Material-Sensitive Effects in Patients with Schizophrenia Compared with Control Subjects

Region of Interest	Brodmann Area(s)	X	Y	Z	ROI *F* Value for Group × Material-Type Interaction	Effect Size of Material Type: Control Subjects	Effect Size of Material Type: Subjects with Schizophrenia
Word > Face in Patients							
Right superior frontal gyrus	6	4	9	66	20.66	.2814	1.6984
Right inferior frontal gyrus	47	41	40	−6	19.57	.6982	1.0879
Right middle frontal gyrus	9	41	14	40	16.56	.1749	1.9145
Left cuneus	18	−21	−92	13	15.39	.1512	1.3336
Left medial frontal gyrus	8	−4	22	43	12.36	.4192	2.2093
Right superior frontal gyrus	6	2	24	60	11.30	.3022	1.0610
Left medial frontal gyrus	6	−44	4	45	9.53	.3238	1.4626
Right inferior frontal gyrus	17	36	17	−3	8.84	.1461	1.7925
Right lentiform nucleus		11	4	−4	7.68	.5736	.7568
Right superior frontal gyrus	10	17	50	23	7.44	.0458	1.3412
Left inferior frontal gyrus	44	−46	3	28	7.39	.7840	1.5454
Left cuneus	18	−5	−101	5	5.89	.7624	2.4614
Face > Word in Patients							
Right inferior temporal gyrus	20	43	−19	−22	9.33	.2708	1.2152

brain regions, whereas high performers require a smaller set of regions (primarily those activated by control subjects) to complete the same tasks.

One potential confound of our study is related to potential medication effects on brain activity and task performance in the schizophrenia group because all but one of our participants were on medications (predominantly atypical antipsychotics). It is possible that we would have found greater evidence for reduced rather than enhanced brain activity if we had studied a sample of unmedicated patients. Furthermore, behavioral performance may have been worse in terms of subsequent recognition in an unmedicated sample. If so, however, the impaired recognition performance may have complicated interpretation of findings of reduced brain activation. Additionally, the gender composition of the groups was quite different, with a disproportionate number of men in the schizophrenia group, which could potentially alter the findings. Subsequent analyses of only the male control and schizophrenia participants, however, revealed identical results to those found with the full sample, thereby reducing the probability that differences in gender composition between groups is driving the results.

In summary, we found increased PFC activity in participants with schizophrenia compared with control subjects in two separate instances. Participants with schizophrenia showed more PFC activity than control subjects during deep encoding of words (when compared with shallow encoding of words), as well as during deep encoding of words (when compared with deep encoding of faces). Our findings add to the growing literature on strategy use in schizophrenia and provide further evidence of the ability of people with schizophrenia to benefit from advantageous encoding conditions. Additionally, we found that strategy orientation enhanced memory-related brain activity in areas such as PFC; however, our schizophrenia patients (especially low performers) activated additional regions of PFC not engaged by control subjects. Further research will be needed to better understand the functional role (or lack thereof) of activation in these additional regions during episodic memory for individuals with schizophrenia. Also, if episodic memory disturbances in schizophrenia are due in part to the failure to apply effective encoding strategies, we need to determine whether this reflects an inability to detect the need for strategies, an inability to select or generate strategies, or problems in the actual applicant component (or some combination of all). Finally, we need to determine the extent to which difficulties in the use of effective retrieval strategies contribute to episodic memory disturbances in schizophrenia.

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