Original Investigation

Functional and Neuroanatomic Specificity of Episodic Memory Dysfunction in Schizophrenia
A Functional Magnetic Resonance Imaging Study of the Relational and Item-Specific Encoding Task

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IMPORTANCE Individuals with schizophrenia can encode item-specific information to support familiarity-based recognition but are disproportionately impaired encoding interitem relationships (relational encoding) and recollecting information. The Relational and Item-Specific Encoding (RiSE) paradigm has been used to disentangle these encoding and retrieval processes, which may depend on specific medial temporal lobe (MTL) and prefrontal cortex (PFC) subregions. Functional magnetic resonance (fMRI) imaging during RiSE task performance could help to specify dysfunctional neural circuits in schizophrenia that can be targeted for interventions to improve memory and functioning in the illness.

OBJECTIVES To use fMRI to test the hypothesis that schizophrenia disproportionately affects MTL and PFC subregions during relational encoding and retrieval relative to item-specific memory processes, and to use fMRI results from healthy individuals serving as controls to establish neural construct validity for RiSE.

DESIGN, SETTING, AND PARTICIPANTS This multisite, case-control, cross-sectional fMRI study was conducted between November 1, 2010, and May 30, 2012, at 5 Cognitive Neuroscience Test Reliability and Clinical Applications for Schizophrenia sites. The final sample included 52 outpatients with clinically stable schizophrenia and 57 demographically matched healthy control participants. Data analysis was performed between February 1, 2013, and May 30, 2014.

MAIN OUTCOMES AND MEASURES Behavioral performance speed and accuracy (d') on item recognition and associative recognition tasks. Voxelwise statistical parametric maps for a priori MTL and PFC regions of interest to test activation differences between relational and item-specific memory during encoding and retrieval.

RESULTS Item recognition was disproportionately impaired in patients with schizophrenia relative to healthy control participants following relational encoding ($F_{1,107} = 4.7$; $P = .03$). The differential deficit was accompanied by reduced dorsolateral PFC activation during relational encoding in patients with schizophrenia compared with healthy control participants ($z > 2.3$; $P < .05$ corrected). Retrieval success (hits > misses) was associated with hippocampal activation in healthy control participants during relational item recognition and associative recognition conditions, and hippocampal activation was specifically reduced in schizophrenia for recognition of relational but not item-specific information ($z > 2.3$; $P < .05$ corrected).

CONCLUSIONS AND RELEVANCE In this unique, multisite fMRI study, results in the healthy control group supported RiSE construct validity by revealing expected memory effects in PFC and MTL subregions during encoding and retrieval. Comparison of schizophrenic and healthy control participants revealed disproportionate memory deficits in schizophrenia for relational vs item-specific information, accompanied by regionally and functionally specific deficits in dorsolateral PFC and hippocampal activation.

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Long-term memory for episodic events can be facilitated by focusing on distinctive features of individual items (ie, item-specific encoding) or examining relationships between multiple items (ie, relational encoding). These encoding processes are of scientific interest because they are mediated by distinct subregions in prefrontal cortex (PFC)[1,2] and they differentially affect representations formed in medial temporal lobe (MTL)[3-5] subregions. Given evidence[6-10] that schizophrenia may disproportionately impair relational memory, an essential next step is to develop an efficient task to differentiate between relational and item-specific processing in individuals with psychiatric disorders.

The Relational and Item-Specific Encoding (RiSE) paradigm was created through the Cognitive Neuroscience Test Reliability and Clinical Applications for Schizophrenia Consortium (http://cntracs.ucdavis.edu). The original paradigm, developed in healthy undergraduate students,[2] was optimized to provide a valid and reliable measure of episodic long-term memory in schizophrenia,[11-13] dissociate specific encoding and retrieval processes, and assist with identification of corresponding brain regions to facilitate translational research aimed at improving cognition as well as clinical and functional outcomes. The RiSE validation study[12] found individuals with schizophrenia to be unimpaired when using a sense of familiarity to retrieve information following item-specific encoding but to be markedly impaired when using familiarity following relational encoding and when trying to recollect information, regardless of the encoding process.

Work is under way with clinical high-risk and first-episode individuals to test whether relational encoding deficits represent a cognitive biomarker for psychosis. However, it is equally important to establish valid imaging biomarkers[14] of relational encoding deficits so that they can be used to identify candidate brain regions for treatment development and outcome assessment. In the present study, we adapted the RiSE paradigm for use in functional magnetic resonance imaging (fMRI). Data were obtained during memory encoding and retrieval in a large sample of healthy individuals used as controls (HCs) and individuals with schizophrenia. Goals of the study were to establish neural construct validity in HCs by demonstrating functionally specific effects in PFC subregions during encoding and MTL subregions during retrieval and, more important, to test the hypothesis that schizophrenia specifically impairs functioning of MTL and PFC subregions associated with relational memory but not with item-specific memory processes. By performing the study at multiple sites with multiple scanners, we also intended to establish whether fMRI effects are sufficiently robust to survive increased variability associated with clinical trial settings.

Methods

Participants

Complete details regarding Cognitive Neuroscience Test Reliability and Clinical Applications for Schizophrenia recruitment and enrollment were reported by Henderson et al.[15] Briefly, participants were recruited nearly equally across 5 sites (eTable 1 in the Supplement): University of California, Davis; Maryland Psychiatric Research Center, University of Maryland; Rutgers University; University of Minnesota Twin Cities; and Washington University, St Louis.

Data were obtained between November 1, 2010, and May 30, 2012, on 60 HCs and 60 individuals with schizophrenia. Data were excluded for 2 patients with excess movement (ie, >0.37 mm of relative frame-to-frame movement), 4 patients and 2 HCs with below-chance performance, and 2 patients and 1 HC with image acquisition errors, leaving a final sample of 57 HCs and 52 people with schizophrenia. Groups were matched for age, sex, handedness, parental educational level, and estimated premorbid intelligence (Wechsler Test of Adult Reading)[16] (Table). Participants with schizophrenia obtained fewer years of school than did HCs, likely reflecting disruption caused by illness onset. Patients were clinically stable, had received a fixed dose of medication for at least 1 month, and were experiencing mild symptoms (Table). All but 4 patients were receiving medication (2 first-generation antipsychotics, 41-second generation antipsychotics, 4 first- and second-

Table. Demographic Characteristics

Characteristic	Mean (SD)		P Value[a]
	HCs (n = 57)	Patients (n = 52)	
Age, y	33.6 (11.5)	33.8 (11.8)	.93
WTAR	37.7 (10.2)	36.0 (9.2)	.34
Education, y			
Participant	14.8 (1.9)	13.1 (1.7)	<.001
Parent	14.9 (3.9)	15.2 (3.2)	.74
Male sex, No. (%)	41 (72)	40 (77)	.55
Right-handed, No. (%)	53 (93)	46 (88)	.41
BPRS score			
Total	NA	42.4 (10.9)	NA
Positive	NA	10.3 (5.2)	NA
Disorganized	NA	6.6 (2.3)	NA
Negative	NA	4.9 (1.8)	NA
UPSA-B score	NA	79.6 (9.6)	NA

Abbreviations: BPRS, Brief Psychiatric Rating Scale; HCs, healthy controls; NA, not applicable; UPSA-B, Brief University of California San Diego Performance-Based Skills Assessment; WTAR, Wechsler Test of Adult Reading.

[a] Two-tailed test.

Figure 1. Illustration of Item-Specific and Relational Test Procedures and Task Stimuli
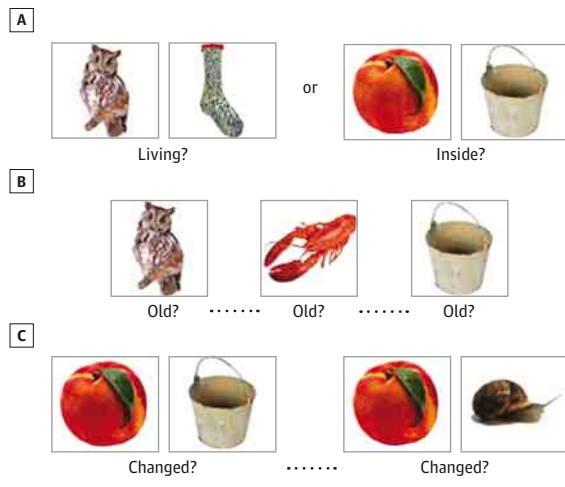
A, Fifty-four object pairs were visually presented while participants made either item-specific encoding responses (left panel) or relational encoding responses (right panel). Conditions alternated (ABAB) between 6 blocks of 9 trials each, with 4-second instruction screens between blocks to minimize alternation demands and maintain task set. B, During item recognition, 54 individual objects from each encoding condition (54 item-specific, 54 relational) were randomly presented with 54 new items, and participants indicated whether each item was old (ie, previously studied). C, During associative recognition, the 27 original relational encoding object pairs were randomly presented with 27 object pairs that had been changed by pairing items from different relational encoding trials (eg, the left object from trial 6 and right object from trial 13), and participants indicated whether each object pair had changed.

generation antipsychotics). After a complete description of the study, written informed consent was obtained. Participants received financial compensation. The study was approved by the institutional review boards at all participating research sites.

Task Design

The design was identical to that of the original RiSE study,[12] with the following exceptions: stimuli were presented in pairs during both encoding conditions (see below), and the item recognition task did not include confidence ratings. Participants completed 1 encoding and 2 retrieval fMRI runs. During encoding (**Figure** 1A), participants alternated between 3 item-specific (eg, Is either object living?) blocks (9 trials each) and 3 relational (eg, Can one object fit inside the other?) blocks (9 trials each) in a "jittered" event-related design. During item recognition (Figure 1B), participants made a 2-button response to indicate whether objects were previously studied (old) or never studied (new). During associative recognition (Figure 1C), participants made a 2-button response to indicate whether object pairs were unchanged (ie, had been studied in the same relational encoding trial) or changed (ie, had been studied in different relational encoding trials). Trials were presented for 3 seconds each, with a 0- to 10-second jittered intertrial interval for both recognition tasks. Participants successfully completed practice versions of the encoding and retrieval tasks prior to scanning. During testing, they were encouraged to respond as quickly and accurately as possible, and guess if unsure. Total scanning duration was approximately 22 minutes.

Imaging Procedures

Images were acquired in a single session (3-T Tim Trio with a 12-channel phased array head coil, Siemens [University of California, Davis; University of Minnesota; Washington University]; a 3.0-T Achieva scanner with an 8-channel head coil, Philips [University of Maryland], or an Allegra scanner with a circularly polarized transmit/receive head coil, Siemens [Rutgers University]) using a consistent protocol across sites (complete details presented in the eMethods in the Supplement).

Preprocessing was accomplished with FMRI Expert Analysis Tool in the FMRIB Software Library (FSL, version 4.1; http://www.fmrib.ox.ac.uk/fsl) using standard procedures, including FieldMap correction. Statistical analysis of subject-level fMRI data was performed between February 1, 2013, and May 30, 2014, using a general linear model implemented in FMRI Expert Analysis Tool. Statistical analysis of group-level data was accomplished by entering parameter estimates from subject-level general linear model analyses into group-level 1-sample and 2-sample t tests in FMRI Expert Analysis Tool for the 1-encoding (relational minus item-specific), 2-item recognition (hits − misses separately for item-specific and relational encoding), and 1 associative recognition (hits − misses) contrast of interest, excluding any nonresponse trials. Because of site differences in scanner characteristics (eTable 2 in the Supplement), research site was added as a covariate in the group-level general linear model designs.

At the group level, we first examined a priori regions in PFC and MTL cortices followed by exploratory whole-brain analyses. Regional analysis goals were twofold: (1) establish neural construct validity and (2) identify group differences. To achieve these goals, voxelwise contrasts were performed within anatomically defined regions for the full sample (ie, across the HC and schizophrenia groups). Anatomic regions of interest (ROIs) for the PFC were identified for the relational minus item-specific encoding contrast with structural masks from the Wake Forest University PickAtlas[17] restricting the mask to activated voxels within left and right dorsolateral PFC (DLPFC) (Brodmann areas 9, 46, and 9/46) and ventrolateral PFC (VLPFC) (Brodmann areas 44, 45, and 47). The MTL ROIs were identified for the hit minus miss contrast during item and associative recognition, and structural masks from the Harvard Oxford Atlas restricted these masks to activated voxels within left and right hippocampus (HI) and posthippocampal gyrus. Using these functionally and anatomically defined PFC and MTL ROIs, voxelwise 1-sample t tests identified activated voxel clusters separately for the HCs and the patients with schizophrenia. Next, 2-sample t tests were used to determine between-group differences within the ROIs. For all analyses, resulting z (gaussianized t) statistic images were subjected to a voxelwise threshold of z greater than 2.3, and a corrected cluster mass significance threshold of $P < .05$ based on gaussian random field theory[18] as implemented in the FMRI Expert Analysis Tool. Any effects outside these ROIs were explored using the FSL whole-brain gray matter mask, with the same thresholding and cluster-correction procedures.

Pearson product moment correlations tested hypothesized relationships between fMRI activation (mean β values in designated ROIs) and performance (d′) within both

Figure 2. Performance Accuracy During Item Recognition
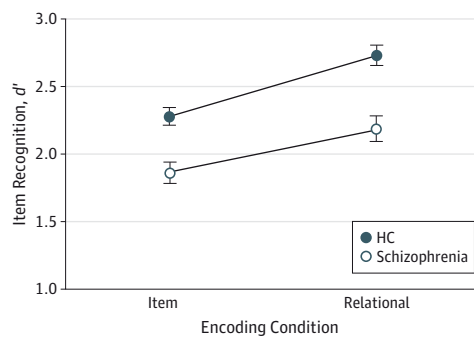
Item recognition was disproportionately impaired in patients with schizophrenia compared with healthy controls (HCs) following relational encoding. Mean values are presented; error bars indicate SE.

groups, and were used in exploratory analyses of relationships between clinical variables, task performance, and fMRI activation in schizophrenia. Fisher z transformation tested for differences in r values. Significance was set at $P < .05$, 2-tailed.

Results

Behavior

Memory Encoding
Participants responded on most encoding trials, with no significant response rate differences between groups (HC, 99%; schizophrenia, 98%; $F_{1,107} = 1.73$; $P = .19$) or any group-by-encoding interaction ($F_{1,107} = 1.91$; $P = .17$). Median reaction times were longer for people with schizophrenia vs the HCs (263.8 milliseconds vs 232.6 milliseconds; $F_{1,107} = 9.3$; $P < .005$) and during relational vs item-specific encoding (285.4 milliseconds vs 221.8 milliseconds; $F_{1,107} = 343.8$; $P < .001$) but did not show any group-by-encoding interaction ($F_{1,107} = 1.8$; $P = .18$). The accuracy of orienting responses remained high in both groups but was slightly lower in people with schizophrenia vs the HCs (75.0% vs 79.2%; $F_{1,107} = 9.5$; $P < .005$) and during relational vs item-specific encoding (72.9% vs 81.4%; $F_{1,107} = 77.9$; $P < .001$). There was no group-by-encoding interaction ($F_{1,107} = 0.01$; $P = .98$). Thus, all participants appeared to be engaged during encoding, and reaction time and accuracy differences between conditions were consistent across groups. Because our interest was in engagement of encoding processes rather than accuracy of frequently equivocal responses (eg, Is an apple that is not on the tree living?), fMRI analysis included all trials in which participants responded.

Memory Retrieval
The group (schizophrenia vs HC)–by-encoding condition (item-specific vs relational) mixed-effects analysis of variance on item recognition (d′) revealed main effects for group ($F_{1,107} = 20.4$; $P < .001$), encoding condition ($F_{1,107} = 178.9$; $P < .001$), and a group-by-encoding interaction ($F_{1,107} = 4.7$; $P = .03$). As illustrated in **Figure 2**, item recognition improved for relational vs

item encoding in both the HC ($t_{56} = 11.8$; $P < .001$) and schizophrenia ($t_{51} = 7.4$; $P < .001$) groups. These effects were qualified, however, by a group-by-condition interaction ($t_{107} = 2.2$; $P = .33$), indicating more severe recognition impairments in schizophrenia following relational encoding (Cohen $d = 0.88$; $F_{1,107} = 21.2$; $P < .001$), vs item-specific encoding (Cohen $d = 0.78$; $F_{1,107} = 16.7$; $P < .001$). Associative recognition was significantly impaired in patients with schizophrenia compared with the HCs (mean [SE], 1.41 [0.11] vs 1.88 [0.10]; $F_{1,99} = 9.53$; $P < .005$). These findings replicate the initial validation study.[12] Examination of clinical variables reported in the Table did not reveal any significant clinical correlations with task performance in the patients with schizophrenia.

fMRI Image Quality
Examination of quality assurance metrics (eTable 1 in the Supplement) revealed a main effect of site ($F_{4,99} = 6.9$; $P < .001$) but no effect of group ($F_{1,99} = 0.3$; $P = .57$) or any group-by-site interactions ($F_{4,99} = 2.0$; $P = .10$). This finding influenced the decision to include site as a covariate in group-level general linear model analyses.

fMRI Relational vs Item Encoding
Contrasts of relational against item-specific encoding across the entire schizophrenia and HC sample revealed robust, bilateral activation in the VLPFC and DLPFC. These regions were interrogated in voxelwise analyses to confirm reliable activation within groups and test for between-group differences.

HC Results
Consistent with findings from a previous study,[2] regions in bilateral DLPFC and VLPFC (**Figure 3**A) showed increased activation during relational compared with item-specific encoding trials. Whole-brain analysis (eTable 2 in the Supplement) revealed these bilateral PFC clusters and a third cluster in parietal and occipital cortices.

Correlational analyses revealed that greater right DLPFC activity during relational encoding was associated with significantly better associative recognition ($r_{56} = 0.35$; $P < .05$). This right DLPFC region did not correlate with item recognition ($r_{56} = 0.14$; $P = .30$); however, the difference in these DLPFC correlations was not significant (Fisher $z = 1.2$; $P = .24$). No correlations were obtained between VLPFC activity and performance in any condition (all $r < .20$).

Patient Results
The contrast between relational vs item-specific encoding revealed PFC activation in the left hemisphere only (Figure 3A). As illustrated, this activation was primarily in VLPFC and extended into ventral portions of DLPFC. Whole-brain analysis (eTable 3 in the Supplement) revealed this left PFC cluster and a second cluster in parietal and occipital cortices. Correlational analyses revealed that greater VLPFC activity during relational encoding was associated with significantly lower associative recognition ($d_{45} = -0.46$; $P < .005$). No significant correlations were observed in DLPFC. Examination of clinical variables in the Table did not reveal any significant correlations in DLPFC. However, higher right hemisphere VLPFC ac-

Figure 3. Prefrontal Cortex (PFC) Activation During Relational vs Item-Specific Encoding
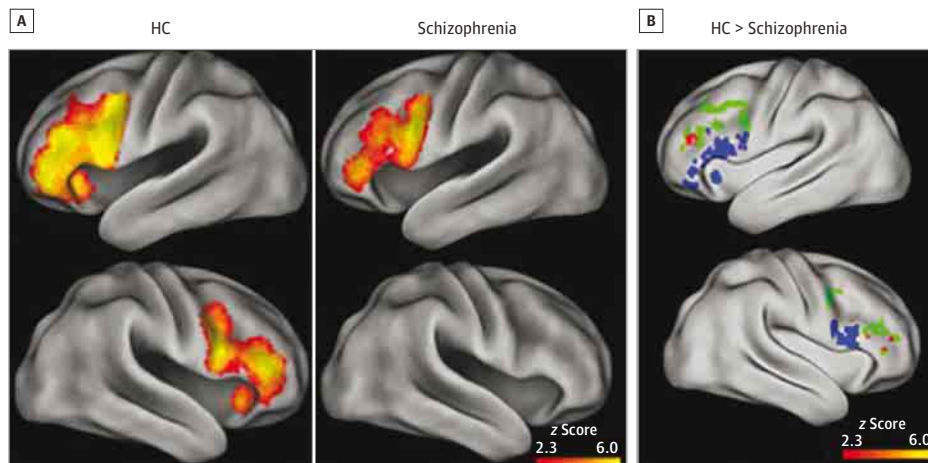
A, Surface rendering of left (top) and right (bottom) hemisphere PFC activation shown separately for healthy controls (HCs) and patients with schizophrenia. Hotter colors reflect greater activation (range, z = 2.3-6.0). B, Significant group differences (HC – schizophrenia) in dorsolateral PFC activation during relational vs item-specific encoding in the left (top) and right (bottom) hemisphere. Group

differences are indicated in red, with hotter colors reflecting greater activation (range, z = 2.3-6.0), and are overlaid on dorsolateral PFC (green) and ventrolateral PFC (blue) regions of interest to illustrate the regional specificity of prefrontal dysfunction in schizophrenia. Surface renderings were performed with Caret, version 5.61, software (http://brainvis.wustl.edu/wiki/index.php/Caret:About).

Figure 4. Hippocampal Activation During Retrieval Success
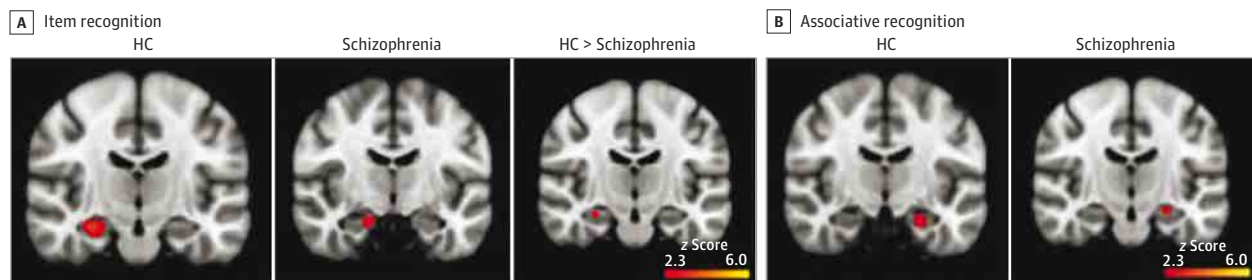
A, Relational encoding for the item recognition task for the healthy control (HC) and schizophrenia groups, including the significant group difference (HC > schizophrenia). B, Hippocampal activation during retrieval success (hits – misses) following relational encoding for the associative recognition task. For

this task, there were no significant between-group differences in hippocampal activation. As in Figure 3, hotter colors reflect greater activation (range, z = 2.3-6.0).

tivity during item-specific encoding correlated with less severe disorganization (r_{46} = −0.40; P < .01).

Group Differences

Between-group contrast of relational minus item-specific encoding revealed suprathreshold clusters in the DLPFC, indicating reduced activation in patients with schizophrenia relative to the HCs (Figure 3B). No group differences were observed in the VLPFC. Whole-brain analysis revealed additional group differences in the right cerebellum (eTable 4 in the Supplement).

fMRI Retrieval Success

Analyses of activity differences between hits and misses during item recognition revealed bilateral suprathreshold activation in the HI and posthippocampal gyrus in the full sample. These regions were interrogated in further analyses described below.

HC Results

Left and right HI activation increased during item and associative recognition hits relative to misses, but only for objects encoded on relational trials (left panels, **Figure 4**). Contrasts for item recognition success for objects encoded on item-specific trials revealed no suprathreshold MTL voxels. Whole-brain analyses did not reveal any additional effects outside of the HI for item or associative recognition following relational encoding. However, successful recognition following item-specific encoding revealed a significant cluster in the left middle and superior frontal gyrus, a second cluster in the parietal and occipital cortices, and a third cluster in the right cuneus and precuneus (eTable 5 in the Supplement).

Patient Results

Patients showed increased left HI activation during successful item recognition following relational encoding and right HI

activation during successful associative recognition (Figure 4). No HI activation was observed following item-specific encoding. Whole-brain analysis of successful item recognition following relational encoding (eTable 6 in the Supplement) revealed bilateral basal ganglia clusters, including effects in the amygdala and parahippocampal gyrus. A third cluster was observed in the left cuneus and bilateral precuneus. Whole-brain analysis of successful associative recognition did not reveal any additional activation. Whole-brain analysis of item recognition success following item-specific encoding (eTable 7 in the Supplement) revealed additional clusters in the left and right posterior cortex, including the bilateral cuneus and precuneus and the inferior parietal cortex. Correlational analysis of clinical variables in the Table revealed that the greater left HI activity was associated with less-severe positive symptom (r_{44} = −0.40; P < .01) and total Brief Psychiatric Rating scale scores (r_{44} = −0.30; P = .46).

Group Differences

Consistent with study hypotheses, HI activation was reduced in people with schizophrenia relative to HCs during successful item recognition following relational encoding (Figure 4A, bottom panel). The associative recognition task did not reveal suprathreshold group differences in HI activation. No group differences were seen in MTL regions during retrieval success for objects that had been encoded on item-specific trials. Exploratory whole-brain analyses did not reveal any additional group differences.

Discussion

Previous research[11-13] established the RiSE as a valid and reliable behavioral measure of episodic memory, capable of revealing differential deficits in relational encoding and recollection-based retrieval associated with reduced functional capacity in schizophrenia. The present study used functional neuroimaging to establish neural construct validity in HC and identify subregions within PFC and MTL memory systems responsible for specific memory deficits in schizophrenia.

Healthy controls exhibited increased DLPFC and VLPFC activation during relational vs item-specific encoding. The DLPFC activity significantly correlated with associative recognition but not with item recognition performance; this result is consistent with research findings[2] from an earlier version of the task. Patterns of HI activation in the HCs during retrieval provided further evidence of neural construct validity. Hippocampal activation increased during successful, compared with unsuccessful, item and associative recognition, but only for items studied during relational encoding. This finding is consistent with basic human and animal research demonstrating a specific role for the HI in relational memory as described in reviews.[3,4,19,20]

Between-group comparisons replicated previous behavioral findings[12] of disproportionate memory impairment in schizophrenia following relational vs item-specific encoding. Most important, the fMRI data showed that these memory deficits were linked to regionally specific reductions in DLPFC activation during relational encoding and to functionally spe-

cific reductions in HI activation during successful recognition following relational encoding.

Results in HCs reflect important anatomic and functional dissociations. Within the PFC, cognitive neuroscience research demonstrates that DLPFC (Brodmann areas 9 and 46) and VLPFC (Brodmann areas 44, 45, and 47)[21,22] support distinct cognitive control processes that facilitate encoding of different, yet complementary, aspects of a given item or event.[1] Activity in the VLPFC increases when one must activate or inhibit goal-relevant features of items (ie, item-specific working memory) to support successful item recognition.[23] In contrast, activity in the DLPFC increases during processing of relationships among items that are active in memory, which, in turn, promotes formation of representations that support retrieval of relational information and associative recognition.[24-30] Within the MTL, several lines of evidence suggest that the HI supports recollection and associative memory,[4,5,31] possibly by binding item and context information.[31] The present results fit this model and substantiate RiSE fMRI neural construct validity, demonstrating that the RiSE fMRI paradigm can be used to dissociate PFC memory control and HI relational binding processes in healthy and clinical populations.

Rather than solely attributing episodic memory deficits in schizophrenia to failed memory consolidation and retrieval in the HI or to disrupted strategic memory control in the PFC, the results of the present study suggest that distinct PFC and HI subregions and mnemonic processes may be disrupted. Patients were most impaired following relational encoding, which demanded recruitment of the DLPFC during encoding and HI during retrieval. In contrast, patients showed less-prominent memory impairment when required to engage the VLPFC to encode item-specific information. This richer and more integrated account of episodic memory in patients with schizophrenia emphasizes the importance of dissociating discrete encoding and retrieval processes and may also help explain variability in the literature[32-34] and arguments about the presence or absence of recognition impairments or arguments about consistency of DLPFC and HI dysfunction.

Based on these results, we speculate that interventions to improve memory in patients with schizophrenia might adopt a 2-step approach. The first is to increase compensatory recruitment of the VLPFC through training in the use of item-specific semantic encoding strategies.[35] However, strategy training alone is unlikely to restore more persistent deficits in relational processing and recollection. Therefore, we also suggest that training in relational processing, possibly in combination with neurostimulation, pharmacologic, or other mechanistic interventions, could improve patients' ability to recruit the DLPFC and HI.[35]

Although the most prominent schizophrenia impairments were observed during relational and associative memory, patients showed a medium to large deficit in item recognition discriminability following item-specific encoding. A similar magnitude deficit was observed in the original RiSE study,[12] but use of confidence ratings in that study allowed us to separately estimate contributions of recollection and familiarity to recognition performance.[36] Those analyses revealed 2 effects: patients experienced global recollection impair-

ment, and there was a specific effect of relational encoding on familiarity-based recognition. Collectively, we believe that these 2 effects can account for many observed memory deficits in schizophrenia. Thus, it is likely that the current recognition discriminability deficit following item-specific encoding was due to patient difficulties in recollection rather than familiarity-based retrieval. This premise can be tested in future fMRI studies by including high, medium, and low confidence ratings during recognition testing, which would allow use of dual-process signal detection models[37] to obtain familiarity and recollection parameter estimates.

The study had other limitations. Because of the multisite design, the patient sample was heterogeneous. However, a potential benefit of this heterogeneity is that it increases generalizability of results to the larger population of individuals with schizophrenia and demonstrates that individuals with different demographic and clinical characteristics are capable of completing RiSE fMRI. In addition, most patients were receiving medication. RiSE studies are under way with clinical highrisk and first-episode patients, many of whom are not currently receiving medication or have never received medication.

Inclusion of these patients will allow investigation of medication and treatment effects. Finally, the associative recognition task was less successful than the item recognition task in revealing significant group differences in HI activation following relational encoding. We believe that this lower level of success was because the task had half as many trials, which reduced sensitivity to detect between-group differences. Future studies may benefit from doubling the number of associative recognition trials.

Conclusions

This multisite fMRI study of episodic encoding and retrieval establishes the neural construct validity of the RiSE paradigm. In addition, the findings suggest that RiSE can successfully detect functionally and neuroanatomically specific deficits in relational memory processes and related DLPFC and HI function in people with schizophrenia across multiple sites using different investigators and imaging environments, similar to what would be encountered in a clinical trials setting.

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