ORIGINAL ARTICLE

Selective Abnormal Modulation of Hippocampal Activity During Memory Formation in First-Episode Psychosis

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Context: Memory is one of the cognitive functions most affected in schizophrenia, with deficits observed from the first episode of psychosis (FEP). Previous studies have indicated that some memory processes may be more affected than others.

Objective: To examine the neural correlates of 3 specific memory processes in FEP by means of functional magnetic resonance imaging (fMRI).

Design: Case-control study.

Setting: Prevention and Early Intervention Program for Psychoses of the Douglas Hospital and Montreal Neurological Institute, McGill University.

Subjects: Twenty-six patients with FEP and 20 healthy controls.

Main Outcome Measures: Behavioral performance and regional brain activity measured during memory encoding by fMRI. Our fMRI design included 3 within-subject contrasts (associative vs item-oriented encoding, encoding of arbitrary vs semantically related image pairs, and successful vs unsuccessful memory encoding) that were then used for group conjunctions and between-group analyses.

Results: Patients with FEP showed normal activation of several brain regions, including the prefrontal cortex, hippocampus, and parahippocampal cortex, during successful memory encoding and associative encoding. In contrast, the hippocampus and surrounding medial temporal areas showed reduced activity during the encoding of arbitrary pairs. This selective dysfunction reflected by abnormal brain activation during encoding was accompanied by a greater deficit for subsequent recognition of arbitrary pairs relative to the semantically related pairs.

Conclusions: This study demonstrated that, in the same group of patients with FEP, the hippocampus could show either normal or abnormal modulation of activation depending on the specific cognitive process that was examined. The normal modulation of hippocampal activation observed during successful memory encoding in FEP argues against a general inability to recruit this region. Instead, the dysfunction was specifically linked to semantic relatedness. This selective deficit seems to affect memory performance in FEP and denotes an important representational problem that may confer greater vulnerability to psychotic disorders and would thus be interesting to examine in high-risk populations.

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THERE IS STRONG EVIDENCE that episodic memory deficits in schizophrenia are related to abnormal activity in the prefrontal cortex and the hippocampus that can be observed during both memory encoding and retrieval[1-4] (see Achim and Lepage[5] and Weiss and Heckers[6] for reviews). This evidence has, however, been based on studies conducted in subjects with chronic schizophrenia in whom confounding factors such as prolonged hospitalizations, long-term medication use,[7,8] and progressive structural brain abnormalities[9-11] could influence the pattern of results. Studying patients in the early course of illness is an effective way to circumvent these confounds.

Behavioral observations suggest that episodic memory is affected early in the course of schizophrenia spectrum psychotic disorders,[12,13] while brain volume data suggest subtle structural abnormalities in the prefrontal cortex[14,15] and the hippocampus[16,17] (see Vita et al[18] for a review) in first-episode psychosis (FEP). However, we know little about the neural correlates of episodic memory problems during the early phase of psychotic disorders. Interestingly, a few recent neuroimaging studies have reported abnormal patterns of prefrontal activation in FEP during the performance of other cognitive tasks such as working memory, cognitive control, and verbal fluency tasks.[19-22]

Functional neuroimaging studies in healthy subjects have led to the identification of specific prefrontal- and hippocampal-dependent processes that contribute to episodic memory encoding and retrieval. In healthy people, the prefrontal cortex and hippocampus have been shown to play a role in successful memory formation (ie, encoding that leads to subsequent memory retrieval).[23-25] The hippocampus is also involved in associating or binding together different components of a learning event.[26-33] Given the evidence that people with schizophrenia are particularly impaired on tests of associative memory retrieval relative to the retrieval of individual items,[34-37] it is likely that the hippocampus plays a role in these associative memory deficits.

The objective of the present functional magnetic resonance imaging (fMRI) study was to examine variations in activation as a result of 3 cognitive manipulations that target hippocampal cortex–dependent and prefrontal cortex–dependent episodic memory encoding processes in a cohort of patients with FEP relative to healthy controls. The 3 cognitive manipulations were designed to examine the effect of associative processing by contrasting associative vs item-oriented encoding, the effect of semantic relatedness processing by contrasting arbitrary vs semantically related pairs of images, and the subsequent memory effect by contrasting successful vs unsuccessful encoding trials.

Because deficits in associative memory are particularly pronounced in schizophrenia,[34-37] we expected patients with FEP to show greater differences in hippocampal and prefrontal activation relative to a control group when associative processing was involved during encoding and to be more impaired on a subsequent recognition test.

In healthy controls, greater associative binding (ie, association of separate components of an episode into an integrated representation), and thus greater hippocampal activation,[32,33] was expected for the arbitrary pairs, relative to the semantically related pairs, because no previously established association was readily available to facilitate encoding of the pairs as a meaningful unit. On the basis of the observation that people with schizophrenia fail to recognize or react to incongruous pieces of information,[38-41] and even tend to classify weak or indirect semantic associations as belonging together,[38,41] we expected that such a modulation of associative binding (and related pattern of hippocampal activation) by image pairs relatedness would be reduced in FEP.

Subsequent memory studies in healthy subjects have consistently reported hippocampal and inferior prefrontal activation.[23-25,42,43] We aimed to determine whether these same brain regions are also active during successful memory formation in FEP.

Finally, although progressive structural changes linked with illness chronicity[9-11] may be largely avoided by studying a FEP sample, it is still important to control for the possible influence of brain volume on brain activation. Considering that the hippocampus is one of our regions of interest from a functional point of view, and that hippocampal volumes are often smaller in schizophrenia, the concurrent assessment of hippocampal volumes in both groups was seen as good way to control for its influence on brain activation.

METHODS

PARTICIPANTS

Patients With FEP

Thirty patients with a first episode of schizophrenia-spectrum psychotic disorder were recruited from the Prevention and Early Intervention Program for Psychoses in Montreal (http://www.douglas.qc.ca/clinical-services/adults/specialized/pepp.asp??l=e). Of these 30 subjects, 4 had to be excluded from the analyses because of technical problems (n=1) or a failure to follow the instructions of the encoding task as evidenced by behavioral results below chance level (n=3). Diagnoses for the remaining 26 subjects with FEP included schizophrenia (n=15), schizoaffective disorder (n=4), and psychosis not otherwise specified (n=7). In addition, 1 subject had a history of major depressive disorder. Diagnosis was based on the Structured Clinical Interview for *DSM-IV*[44] conducted by a trained interviewer and confirmed through consensus between 2 senior psychiatrists (A.K.M. and R.J.).

Imaging was performed as soon as the subjects were stable enough to be included in the study. For that purpose, the suitability of a patient to participate was reassessed on a weekly basis until the clinical and research team agreed that acute symptoms would not interfere with the protocol, which implies not moving for more than an hour. Subjects with FEP underwent imaging within a few months after initiation of antipsychotic therapy (median, 17 weeks; mean, 25 weeks; range, 0-83 weeks).

At the time of imaging, 22 subjects with FEP were taking antipsychotic medication (risperidone [n=11; mean dose, 2.11 mg], olanzapine [n=5; mean dose, 10.50 mg], quetiapine fumarate [n=2; mean dose, 325 mg]; clozapine [n=1; dose, 300 mg], haloperidol [n=1; dose, 1.5 mg], and mixed [n=2]) and 4 were free of antipsychotic medication. In addition, 5 subjects with FEP were taking antidepressants (paroxetine hydrochloride [n=3; mean dose, 23.33 mg], venlafaxine hydrochloride [n=2; mean dose, 131.25 mg]), 2 were taking benzodiazepines (clonazepam [mean dose, 0.50 mg]), and 2 were taking anticholinergics (benztropine mesylate [mean dose, 1.50 mg]). The 2 subjects taking anticholinergics did not exhibit more prominent memory impairments than the rest of the group; in fact, they performed above the mean of their group on our recognition memory test (see description of the task in a subsequent section). There also was no significant difference in behavioral performance between patients taking antipsychotic medication with (quetiapine, olanzapine, and clozapine) or without (risperidone and haloperidol) reported anticholinergic potency.[45] For the 2 subjects taking benzodiazepines, one performed above average and the other performed slightly below average on our recognition test.

Healthy Controls

Twenty healthy control subjects were recruited by means of advertisements placed in local newspapers. A modified version of the Structured Clinical Interview for *DSM-IV* Axis I Disorder was used to rule out the possibility of current psychiatric illness. Control subjects reported no current or previous history of neurologic disease or head trauma causing loss of consciousness and no first-degree family member with

schizophrenia or schizophrenia-spectrum psychosis. Groups were matched for age, sex, and parental socioeconomic status as assessed with the Hollingshead 2-factor index of social position.[46]

After a complete description of the study, written informed consent was obtained from all participants. The protocol was approved by the institutional review boards of the Douglas Hospital and Montreal Neurological Institute.

ASSESSMENT OF DEMOGRAPHIC, CLINICAL, AND NEUROPSYCHOLOGICAL DATA

Handedness was assessed with the Edinburgh Inventory,[47] and subjects were classified as right-handed, moderately right-handed, ambidextrous, moderately left-handed, or left-handed on the basis of their laterality quotient (cutoff of –±70 to consider someone as fully right- or left-handed and –±50 to considered someone as moderately right- or left-handed). Handedness was, however, not included as a matching criterion because a higher proportion of non–right-handedness (ie, increased left-handedness and mixed-handedness) is often observed in patients with psychotic disorders.[48,49] Moreover, in healthy subjects, mixed-handedness has been reported to be associated with higher scores of schizotypy,[50] and we did not want to bias our control group by purposely recruiting non–right-handed subjects.

All subjects with FEP were administered a structured protocol that included symptom ratings using the Scale for the Assessment of Positive Symptoms,[51] Scale for the Assessment of Negative Symptoms,[52] Calgary Depression Scale,[53] and Hamilton Anxiety Scale.[54] For most subjects (22 of 26 subjects), the clinical evaluation was performed within a month of the imaging session (median, 3 weeks; mean, 3 weeks; range, 0-30 weeks). Neuropsychological assessment was performed in both the FEP group and the control group to better characterize the cognitive profile of our groups. For that purpose, we used a short version of the Wechsler Adult Intelligence Scale, Third Edition,[55] the Wechsler Memory Scale, Third Edition,[56] the Stroop test,[57] the D2 Test of Attention,[58] and the Trail Making Test A and B.[59] The neuropsychological battery was administered a mean of 12.5 weeks apart from the imaging session (median, 6 weeks; range, 0-66 weeks).

ANALYSES OF DEMOGRAPHIC AND NEUROPSYCHOLOGICAL DATA

After the normality of the distributions for each of the demographic and neuropsychological variables was verified, outliers were excluded (1 subject in the FEP group for the Stroop color test), and normality correction was carried out when necessary (for the Wechsler Memory Scale Visual Reproduction, digit span, and Trail Making Test B completion time). Next, *t* tests were used to assess between-group differences, except for the sex variable, for which we used a χ^2 test, and handedness categories, for which we used a Mann-Whitney rank sum test.

IMAGING PROCEDURE

Imaging was carried out at the Montreal Neurological Institute on a 1.5-T system (Sonata; Siemens, Malvern, Pennsylvania). A structural T1 volume was acquired for each subject by means of a 3-dimensional spoiled gradient echo acquisition with sagittal volume excitation ($1 \times 1 \times 1$-mm voxels). Two fMRI sessions followed, and each consisted of 214 T2*-weighted volumes acquired with blood oxygenation level–dependent contrast (repetition time, 2130 milliseconds; echo time, 50 milliseconds; flip angle, 90°; 25 interleaved sections; $2 \times 2 \times 5$-mm voxels). Functional volumes were acquired parallel to the anterior-posterior commissural plane.

STIMULI AND BEHAVIORAL TASK

Stimuli consisted of pairs of clip art images (representing common objects, foods, or animals) arranged side by side on the screen. For the fMRI task, each of the 2 sessions comprised 56 different pairs, with 28 being arbitrarily paired (ie, formed of semantically unrelated items) and 28 representing semantically related items. This manipulation will be referred to as the *semantic relatedness manipulation*. To confirm the classification of the pairs as either arbitrary or related, 6 healthy subjects (who did not participate in the fMRI study) were shown an initial series of pairs and asked to judge whether each pair represented related entities. Only the pairs for which there was an agreement in at least 5 of 6 subjects were used in the final version of the task.

The pairs were presented through a projector and mirror system, with each trial consisting of the appearance of an encoding cue for 3 seconds followed by a pair of images for 3 seconds. The encoding cues served to orient the subject to perform 1 of 2 different encoding tasks. Half of the cues promoted the adoption of an associative encoding strategy (ie, subjects were asked to compare the 2 images and answer which of the 2 would be bigger in real life size), and the other half promoted the adoption of a deep item-oriented encoding strategy (ie, subjects were asked to judge whether ≥ 1 of the images represented a living entity). This manipulation will be referred to as the *encoding strategy manipulation*. It should be noted that most (23 of 28) of the pairs that had to be categorized as living included only 1 living stimulus, and that the position of that living stimulus in the pair (ie, left or right of the fixation cross) was counterbalanced across the different pairs, minimizing the chances that the subjects could have performed the task correctly while attending to only 1 stimulus of the pair. The 2 types of semantic relatedness (arbitrary and semantically related) and the 2 types of encoding strategies (associative and item-oriented) were mixed randomly, and fixation crosses lasting from 1 to 4 seconds were randomly presented between the encoding trials. Subjects gave their responses by means of a fiberoptic response pad.

Following the 2 memory encoding sessions, recognition memory was assessed in 2 sessions (not accompanied by fMRI) by presenting all the pairs previously encoded along with an equal number of distracters (pairs formed of 2 new items, half being arbitrarily paired and half semantically related), for a total of 112 pairs per recognition session. The recognition performance on each recognition trial for previously encoded pairs served to classify the encoding trials as either successful or unsuccessful. This distinction between successful and unsuccessful encoding trials will be referred to as the *subsequent memory effect*.

All subjects performed a short version of the encoding and recognition tasks (with a different set of image pairs) before scanning to ensure that they were well understood.

Although we did not use an associative recognition test (which typically requires the subject to distinguish between intact and rearranged pairs of items) in this study, an associative recognition test was used in a separate behavioral study[60] using the exact same encoding task followed by an associative recognition test. The results from that study showed that associative recognition was better after our associative encoding

task than after our deep item-oriented encoding task, consistent with our assumption that our associative encoding instructions promote association memory to a greater extent than do our item-oriented encoding instructions.

BEHAVIORAL ANALYSES

Analyses of variance (ANOVAs) for 2 encoding strategies (associative vs item-oriented) × 2 semantic relatedness (arbitrary pairs vs semantically related pairs) × 2 groups (control vs FEP) were performed on the means for performance and response time during both encoding and recognition. During encoding, performance was calculated as the percentage of correct answers to the encoding questions (ie, the questions that the subjects had to answer to promote either associative or item-oriented encoding). During recognition, the hit rate was chosen as our measure of recognition memory accuracy because it allowed us to evaluate the effect of encoding strategy on subsequent retrieval. We also examined the false alarm rates, but for this analysis only the effect of semantic relatedness and group could be included in the ANOVA.

fMRI ANALYSES

Functional analyses were performed with the SPM2 software (Wellcome Department of Cognitive Neurology, London, England; http://www.fil.ion.ucl.ac.uk/spm). Image preprocessing was done according to standard procedures. Briefly, images were time corrected to account for differences in sampling times for different sections, realigned to the first volume to correct for movement, spatially normalized to the EPI (echo planar imaging) template, and smoothed with an 8-mm full-width half-maximum gaussian kernel. Low-frequency temporal drifts were removed by applying a high-pass filter. Data were analyzed by the general linear model, in which individual events were modeled by a canonical hemodynamic response function. Before the analyses for each individual subject were performed, the movement correction logs were examined to ensure that none of the subjects presented movements greater than 5 mm or 5°. None of our subjects met that threshold.

Two design matrixes were produced for each subject (both including the 2 encoding sessions in the same design matrix), one for the encoding strategy and semantic relatedness effects and another one for the subsequent memory effect contrast. The 2 design matrixes differed in terms of the events that were modeled.

To assess the effect of *encoding strategy* (associative vs item-oriented) and *semantic relatedness* (arbitrary vs related pairs), 4 types of trials were modeled for each encoding session: (1) associative encoding of arbitrary pairs, (2) associative encoding of related pairs, (3) item-oriented encoding of arbitrary pairs, and (4) item-oriented encoding of related pairs. Six covariates corresponding to the movement parameters (obtained from the realignment procedure) for each fMRI session were also included in the design matrix.

For the *subsequent memory effect*, 2 types of events were modeled for each encoding session: (1) successful encoding (ie, encoding of subsequently recognized pairs) and (2) unsuccessful encoding (ie, encoding of subsequently forgotten pairs). Here again, the 6 covariates corresponding to the movement parameters for each fMRI session were included in the design matrix. For an fMRI session to be included in the within-subject contrast between successful and unsuccessful encoding trials, it had to include at least 5 events of each type. For 3 controls and 3 subjects with FEP, only 1 of the 2 encoding sessions was included in the computation of the within-subject contrast because the other session did not include at least 5 unsuccessful trials. Moreover, 3 control subjects and 1 subject with FEP had to be completely excluded from the fMRI analyses because they showed fewer than 5 unsuccessful encoding trials in both encoding sessions, leaving a group of 17 controls and 25 subjects with FEP for the subsequent group analyses.

These analyses led to 3 main contrasts of interest, namely, the contrast between associative and item-oriented encoding trials (effect of encoding strategy), the contrast between arbitrary pairs and related pairs (effect of semantic relatedness), and the contrast between successful and unsuccessful encoding trials (subsequent memory effect). Within-group analyses were also performed for each contrast by means of a random-effects model, and conjunction analyses were applied to identify the regions showing significant activation in both groups. Then, between-group effects for each of these contrasts were examined with 2-sample *t* tests by means of a random-effects model. These analyses were performed with a threshold of $P < .001$ uncorrected and a cluster extent of 10 contiguous voxels ($2 \times 2 \times 2$ mm). Because of our a priori hypotheses in the hippocampus and inferior prefrontal cortex, clusters in these regions were also examined to determined whether they survived a threshold of $P = .05$ corrected for multiple comparisons by means of the random field theory approach.[61] These corrections were based on a volume of 4300 mm^3 (corresponding to 538 voxels) for the left and right hippocampus, and 9000 mm^3 (corresponding to 1125 voxels) for the left and right inferior prefrontal cortex.

ANALYSES OF HIPPOCAMPAL VOLUME

A preprocessing algorithm was first applied to the T1 volumes that included a correction for magnetic field nonuniformities, linear stereotaxic transformation into coordinates based on the Talairach atlas, and intensity normalization. Segmentation of the left and right hippocampus was then manually performed with the Display software using the protocol described by Pruessner et al.[62] The volumes of the left and right hippocampus were then compared between the 2 groups by means of independent sample *t* tests and a threshold of $P < .05$ (2-tailed).

RESULTS

DEMOGRAPHIC, CLINICAL, AND NEUROPSYCHOLOGICAL RESULTS

Demographic data for both groups are presented in **Table 1**, along with clinical and neuropsychological data. There were no significant differences between the 2 groups on demographic variables. As expected, the control group had a higher IQ than the FEP group and performed better on several tests, including the episodic memory measures from the WMS-III, the D2 test of attention, and the Stroop tests.

BEHAVIORAL RESULTS

The behavioral data for encoding and recognition are presented in **Table 2** and **Table 3**, respectively.

Encoding

Before the ANOVA was performed, an outlier in the control group was excluded from the behavioral analyses because this subject performed at chance level for item-

Table 1. Sociodemographic, Clinical, and Neuropsychological Data for the FEP and Healthy Control Groups

	FEP[a]		Controls[a]		*P* Value (2-Tailed)
	Mean (SD)	Range	Mean (SD)	Range	
Age, y	22.6 (3.4)	18-29	23.6 (3.3)	18-32	.31
Sex, No. (%)					.37
Female	8 (31)		9 (45)		
Male	18 (69)		11 (55)		
Parental socioeconomic status, No. (%)					.25
Upper	1 (4)		0 (0)		
Upper middle	6 (23)		7 (35)		
Middle	5 (19)		6 (30)		
Lower middle	7 (27)		5 (25)		
Lower	7 (27)		2 (10)		
Handedness category, No. (%)					.09
Right	18 (69)		18 (90)		
Moderately right	3 (12)		1 (5)		
Ambidextrous	4 (15)		1 (5)		
Moderately left	0		0		
Left	1 (4)		0		
WAIS-III IQ	94.3 (15.3)	69-121	108.4 (9.2)	96-128	<.001
Episodic memory					
WMS-III logical memory (I + II)	56.2 (20.5)	15-95	79.5 (19.3)	38-110	<.001
WMS-III visual reproduction (I + II)[a]	162.7 (28.9)	105-207	194.4 (14.7)	151-208	<.001
Working memory					
Digit span[b]	16.7 (4.0)	8-24	17.2 (4.1)	12-27	.63
Spatial span	16.5 (4.0)	9-23	18.5 (2.8)	13-24	.08
Attention					
D2 Test of Attention, CP	155.1 (52.2)	61-279	193.9 (34.6)	141-263	.007
Trail Making Test A, completion time, s	34.3 (10.7)	19-55	32.9 (9.8)	18-57	.66
Executive functioning					
Stroop word	92.2 (15.0)	62-122	103.2 (11.3)	80-125	.01
Stroop color	67.6 (11.3)	49-84	77.1 (8.7)	65-99	.004
Stroop word-color	41.5 (11.6)	20-68	49.7 (9.5)	29-69	.02
Trail Making Test B, completion time, s[b]	75.5 (32.2)	34-162	63.4 (16.0)	31-101	.23
SAPS[c]	11.2 (9.3)	0-32			
SANS[c]	12.9 (10.3)	0-34			
Calgary Depression Scale	1.2 (2.1)	0-9			
Hamilton Anxiety Scale	2.3 (2.6)	0-10			
Duration of untreated psychosis, No. of weeks[d]	57.7 (81.0)	1-294			

Abbreviations: CP, concentration performance; FEP, first-episode psychosis; SANS, Scale for the Assessment of Negative Symptoms; SAPS, Scale for the Assessment of Positive Symptoms; WAIS-III, Wechsler Adult Intelligence Scale, Third Edition; WMS-III, Wechsler Memory Scale, Third Edition.

[a] Data presented are scores unless otherwise indicated.

[b] Although a correction for nonnormality of the distribution had to be applied before the statistical tests were performed for these variables, the means and standard deviations are presented as raw data (ie, before correction for the nonnormal distribution) and should be interpreted with caution.

[c] SAPS and SANS scores are composite totals for which the global ratings were not included.

[d] Number of weeks between first psychotic symptoms and initiation of treatment.

oriented encoding of arbitrary pairs. This subject was debriefed after scanning and reported giving a positive response only when both items were alive (in the original instructions, only 1 was required to be alive). This subject's results were kept, however, for the fMRI analyses because the distinction between associative and deep item-oriented encoding was not compromised by this pattern of responding. Even after exclusion of that subject, encoding performance was not normally distributed and a logarithmic transformation was applied before the ANOVA was conducted. These corrected data showed a significant effect of semantic relatedness ($F_{1,43}$=25.7, P<.001) and a significant effect of group ($F_{1,43}$=20.0, P<.001), but no significant effect of encoding strategy and no significant interactions.

Exploratory post hoc analyses showed that, although the FEP group had more unanswered encoding questions overall (150 in FEP vs 14 in the control group), the difference in the proportion of unanswered encoding questions between the successful and unsuccessful encoding trials did not differ between the control group and the FEP group (P=.41, 2-tailed).

With respect to the encoding response times, we observed significant effects of encoding strategy ($F_{1,44}$=28.6, P<.001), semantic relatedness ($F_{1,44}$=5.01, P=.03), and group ($F_{1,44}$=4.96, P=.03), and a significant interaction of encoding strategy × semantic relatedness ($F_{1,44}$=15.3, P<.001). The other interactions did not reach significance. The encoding strategy × semantic relatedness interaction reflected that the response times were shorter for related pairs than for arbitrary pairs when the subjects were responding to the item-oriented encoding cues ($F_{1,44}$=20.3, P<.001; effect size [ES] d=0.66), but did not significantly differ when the sub-

Table 2. Encoding Performance and Response Time for the FEP and Healthy Control Groups

	Mean (SD)			
	Associative		Item-Oriented	
Encoding	Arbitrary	Related	Arbitrary	Related
Performance[a]				
Control	0.94 (0.05)[b]	0.96 (0.03)[b]	0.90 (0.11)[b]	0.96 (0.05)[b]
FEP	0.88 (0.08)[b]	0.91 (0.07)[b]	0.83 (0.14)[b]	0.88 (0.10)[b]
Response time, ms				
Control	1367 (161)	1400 (175)	1316 (145)	1243 (162)
FEP	1482 (180)	1493 (143)	1409 (187)	1329 (170)

Abbreviation: FEP, first-episode psychosis.
[a] Data are percentages of correct answers, presented as a proportion of the total possible.
[b] The means and standard deviations represent the raw data (ie, before correction for the nonnormal distribution) and should be interpreted with caution.

Table 3. Recognition Performance and Response Time for the FEP and Healthy Control Groups

	Mean (SD)					
	Associative		Item-Oriented		False Alarm Rate	
Recognition	Arbitrary	Related	Arbitrary	Related	Arbitrary	Related
Performance[a]						
Control	0.88 (0.07)	0.89 (0.07)	0.83 (0.10)	0.79 (0.08)	0.08 (0.05)[b]	0.03 (0.03)[b]
FEP	0.80 (0.13)	0.85 (0.13)	0.72 (0.14)	0.74 (0.17)	0.09 (0.07)[b]	0.04 (0.04)[b]
Response time, ms						
Control	1115 (143)	1034 (153)	1192 (167)	1134 (177)	1525 (217)	1614 (465)
FEP	1332 (202)	1176 (222)	1367 (230)	1212 (192)	1717 (404)	1510 (334)

Abbreviation: FEP, first-episode psychosis.
[a] Data are percentages of correct answers, presented as a proportion of the total possible.
[b] The means and standard deviations for false alarm rate represent the raw data (ie, before correction for the nonnormal distribution) and should be interpreted with caution.

jects were responding to the associative encoding cues ($F_{1,44}$=1.51, P=.23; ES d=0.18).

Recognition

The ANOVA on hit rate showed a significant effect of encoding strategy ($F_{1,44}$=42.3, P<.001) and of group ($F_{1,44}$=5.5, P=.02), as well as a significant semantic relatedness × group interaction ($F_{1,44}$=7.16, P=.01). The other effects or interactions did not reach significance. The semantic relatedness × group interaction reflected that the 2 groups differed in their recognition performance for the arbitrary pairs (t_{44}=2.72, P=.01), corresponding to an ES d=0.81, but did not significantly differ for the related pairs (t_{44}=1.32, P=.19), corresponding to an ES d=0.39.

Before the ANOVA for the false alarm rate was performed, 2 outliers were excluded from the FEP group, and data were transformed by a logarithmic function to correct the lack of normality of the distributions. This analysis showed a significant effect of semantic relatedness ($F_{1,42}$=43.5, P<.001), but no significant effect of group and no significant group × semantic relatedness interaction.

As for the recognition response times (for old items only), we observed significant effects of encoding strategy ($F_{1,44}$=18.1, P<.001), semantic relatedness ($F_{1,44}$=46.0, P<.001), and group ($F_{1,44}$=9.79, P=.003), and a significant semantic relatedness × group interaction ($F_{1,44}$=6.79, P=.01). The other interactions did not reach significance. The semantic relatedness × group interaction reflected that the between-group difference was highly significant for the arbitrary pairs (t_{44}=3.82, P<.001), corresponding to an ES d=1.14, with a significantly smaller ES of d=0.63 for the related pairs (t_{44}=2.12, P=.04).

For the false alarm rates, only subjects who had committed at least 1 false alarm for the arbitrary pairs and 1 for the related pairs (14 controls and 19 patients with FEP) could be included in the response time analyses. A group × semantic relatedness ANOVA with these subjects did not show any significant effect or interaction.

HIPPOCAMPAL VOLUME RESULTS

The mean hippocampal volumes are expressed in cubic millimeters (with standard deviations in parentheses) after linear stereotaxic transformation to a template brain. The volumes for the control group and the FEP group were 4215 (562) mm^3 and 4080 (481) mm^3, respectively, for the left hippocampus and 4151 (503) mm^3 and 4000 (453) mm^3, respectively, for the

Table 4. Results of Between-Group Analysis and Conjunction Analysis for Contrast Between Associative Encoding and Item-Oriented Encoding[a]

Cluster Size	*t* Value	Talairach Coordinates			Hemisphere	Region	*t* Value	
		x	y	z			Controls	FEP
					Controls > FEP			
14	3.86	–42	16	–24	Left	Superior temporal	1.34	–4.69
					Conjunction (FEP ∩ Controls)			
25	2.42	–50	6	28	Left	Inferior frontal/precentral	2.88	2.42
177	**3.18**	**50**	**8**	**30**	**Right**	**Inferior frontal/precentral**	**3.66**	**3.18**
279	2.81	–4	–58	14	Left	Posterior cingulate	2.81	2.88
3516[b]	4.13	26	–38	–16	Right	Fusiform/parahippocampal	5.73	4.13
4863[c]	5.12	–28	–46	–14	Left	Fusiform/parahippocampal	5.12	5.27
3516[b]	5.64	46	–74	22	Right	Middle temporal/occipital	5.91	5.64
14	2.10	30	–52	52	Right	Superior parietal	2.10	2.63
4863[c]	4.87	–28	–90	2	Left	Occipital	5.33	4.87

Abbreviation: FEP, first-episode psychosis.

[a]The cluster size represents the number of voxels. The x, y, and z coordinates of local maxima are listed according to the Talairach coordinate system. The clusters surviving the corrected threshold in our regions of interest are highlighted in bold. The *t* values reported in the last 2 columns were extracted from the within-group analyses for the control group and for the FEP group. The *t* value reported for the conjunction analysis corresponds to the lowest *t* value between the 2 groups. There was no region of significant differences in activation for the "FEP greater than controls" contrast.

[b]These peaks belong to the same cluster of activation.

[c]These peaks belong to the same cluster of activation.

right hippocampus. A contrast of volumes showed no significant differences between the 2 groups on the left ($t=0.41$, $P=.69$, 2-tailed; ES d=0.12) or the right hippocampus ($t=0.64$, $P=.53$, 2-tailed; ES d=0.20). Therefore, the difference in hippocampal volumes likely had little influence on the observed pattern of activation and was not retained for subsequent fMRI analyses.

fMRI RESULTS

Associative vs Item-Oriented Encoding Strategies

Results on conjunction and group comparisons for the associative vs item-oriented encoding strategies are presented in **Table 4** and **Figure 1**. The conjunction analysis demonstrated the following brain regions to show greater activation for associative encoding in both groups: inferior prefrontal cortex at the junction of the precentral gyrus bilaterally, right middle temporal gyrus, right superior parietal lobule, left fusiform gyrus, and posterior cingulate.

Compared with subjects with FEP, the control group showed greater activation during associative encoding in the left superior temporal gyrus. No brain region showed greater activation in the FEP group for this contrast.

Arbitrary vs Semantically Related Stimulus Pairs

The conjunction and group comparisons for the arbitrary vs related pairs contrast are presented in **Table 5** and **Figure 2**. The conjunction analysis demonstrated activation in the right thalamus, right fusiform gyrus, left middle temporal gyrus, and bilateral occipital lobes in both groups.

The between-group comparisons showed greater activation in the control group relative to the FEP group in large regions of the medial temporal lobes, encompassing the amygdala, hippocampus, and parahippocampal gyrus bilaterally, as well as bilateral insula, lateral temporal cortex, and cerebellum. The reverse comparison did not show any brain regions showing greater activation in the FEP group.

Subsequent Memory Effect

The conjunction and group comparison results for the subsequent memory effect are presented in **Table 6** and **Figure 3**. The conjunction analysis showed significant subsequent memory effect activation in both groups in several brain regions, including the inferior prefrontal cortex bilaterally, left hippocampus, and parahippocampal gyrus bilaterally.

None of the brain regions showed greater subsequent memory effect activation in the control group relative to the FEP group. Instead, the FEP group showed significantly greater activation for this contrast in the left sensorimotor cortex, left precuneus, right superior temporal gyrus, right insula, and right thalamus.

COMMENT

The current study examined prefrontal- and hippocampal-dependent memory encoding processes in a sample of patients treated for their FEP and a group of matched healthy controls. Contrary to our initial hypotheses, only the manipulation of semantic relatedness showed an abnormal pattern of hippocampal activity in subjects with FEP relative to healthy controls. Moreover, this group (FEP vs controls) × semantic relatedness (arbitrary pairs vs related pairs) interaction observed in the

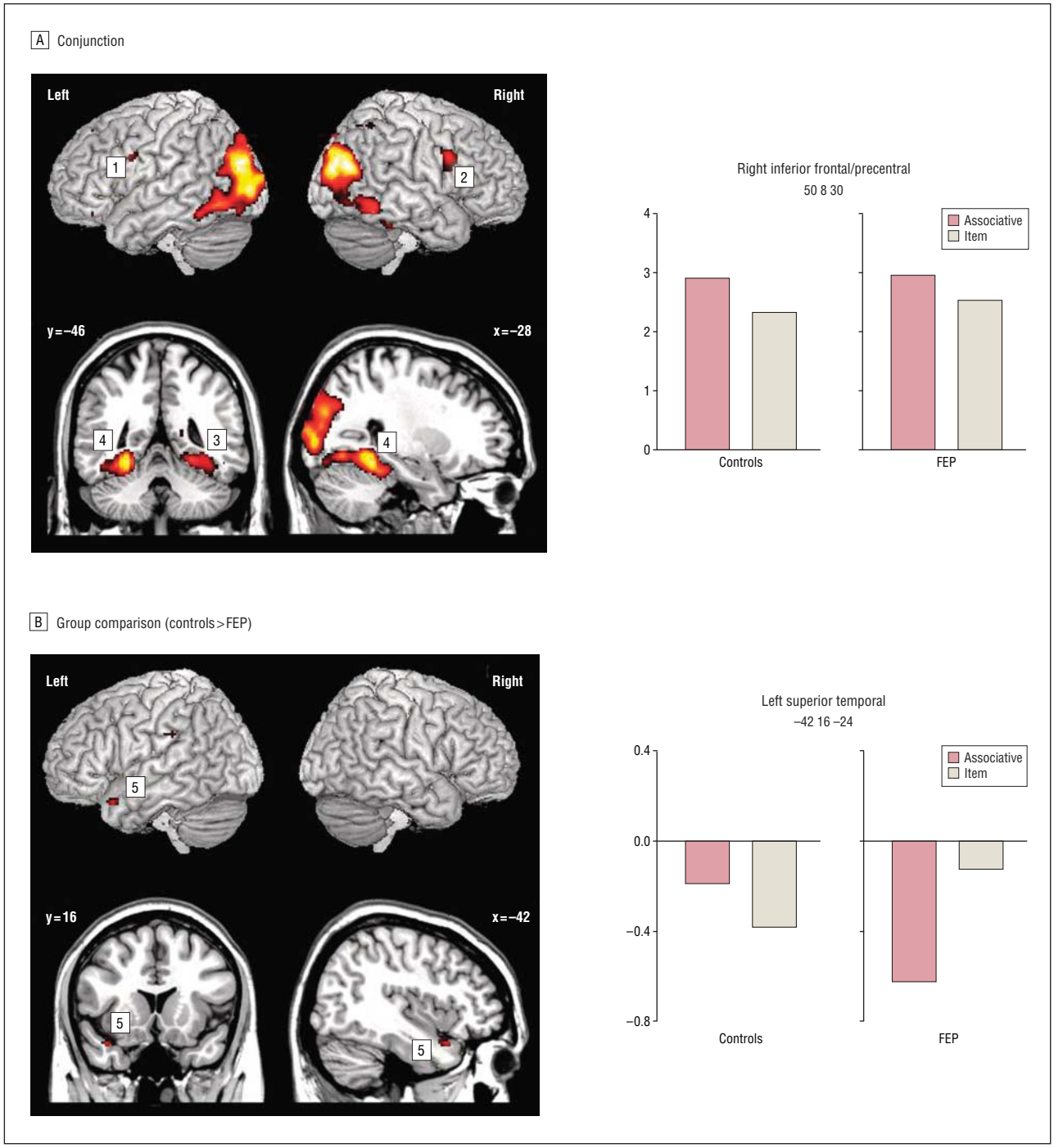

Figure 1. Results from the analyses of associative relative to item-oriented encoding and parameter estimates of selected peaks. A, Conjunction analysis showing the regions of activation common to both groups. B, Between-group analysis showing the regions that were significantly more active in the control group relative to the first-episode psychosis (FEP) group. Insets, The insets in both parts represent the Talairach coordinates x, y, and z, that is, right to left, anterior to posterior, and superior to inferior, respectively. 1, Left inferior frontal/precentral cortex; 2, right inferior frontal/precentral cortex; 3, right fusiform/parahippocampal gyrus; 4, left fusiform/parahippocampal gyrus; and 5, left superior temporal gyrus.

pattern of brain activation during memory encoding was complemented by a similar interaction in behavioral performance during the subsequent recognition test. In contrast, our other 2 manipulations (ie, associative processing and successful memory formation) yielded normal patterns of prefrontal and hippocampal activation in FEP. Taken together, these results suggest that forming new associations in the absence of semantic relations is selectively impaired in FEP. Structural differences cannot account for this finding because the 2 groups did not significantly differ in terms of their hippocampal volumes. Hence, the current study provides a novel characterization of normal and impaired memory encoding processes and their neural correlates in FEP.

Table 5. Results of Between-Group Analysis and Conjunction Analysis for Contrast Between Arbitrary Pairs and Related Pairs[a]

Cluster Size	*t* Value	Talairach Coordinates x	y	z	Hemisphere	Region	*t* Value Controls	*t* Value FEP
					Controls > FEP			
446[b]	4.83	–32	–2	–36	Left	Entorhinal parahippocampal	4.5	–2.46
446[b]	4.56	–36	–10	–40	Left	Parahippocampal/fusiform	4.73	–1.76
446[b]	4.31	–30	–14	–32	Left	Parahippocampal	2.9	–3.28
53	4.30	–28	–28	–18	Left	Parahippocampal	1.95	–4.81
35	**4.15**	**–18**	**–34**	**4**	**Left**	**Thalamus/hippocampus**	**3.49**	**–2.70**
296[c]	4.76	28	4	–38	Right	Entorhinal/parahippocampal	4.5	–1.29
296[c]	**5.33**	**30**	**–8**	**–26**	**Right**	**Hippocampus**	**5.38**	**–1.85**
43	4.41	36	–10	–40	Right	Parahippocampal/fusiform	4.14	–1.95
11	3.57	–32	10	–28	Left	Superior temporal	3.13	–1.64
18	3.76	50	10	–40	Right	Middle temporal	1.48	–4.69
14	3.60	52	–4	–12	Right	Superior temporal	2.01	–3.30
296[c]	4.23	38	–16	–24	Right	Fusiform	4.55	–2.23
219[d]	4.31	42	–60	4	Right	Middle temporal	4.73	–1.06
219[d]	4.42	48	–66	–2	Right	Inferior temporal	6.21	0.47
42	4.26	–28	–10	–8	Left	Putamen	2.66	–3.52
95[e]	4.10	–42	–16	16	Left	Insula	3.84	–3.16
95[e]	3.65	–38	–24	16	Left	Insula	2.9	–2.23
16	3.59	42	–12	12	Right	Insula	2.84	–2.59
10	3.54	38	–12	24	Right	Insula	2.6	–2.46
89[f]	3.75	12	–50	–14	Right	Cerebellum	3.43	–2.11
89[f]	4.05	6	–64	–16	Right	Cerebellum	2.96	–3.05
					Conjunction (FEP ∩ Controls)			
95	2.58	–40	–82	16	Left	Middle temporal	3.25	2.58
395	5.44	42	–42	–20	Right	Fusiform	5.44	5.97
98	3.19	–42	–74	–8	Left	Inferior occipital	3.19	3.28
21	2.48	–24	–96	8	Left	Middle occipital	2.48	2.58
600	3.87	52	–76	0	Right	Middle occipital	4.38	3.87
171	3.16	6	–18	–2	Right	Thalamus/red nucleus	3.19	3.16

Abbreviation: FEP, first-episode psychosis.

[a] The cluster size represents the number of voxels. The x, y, and z coordinates of local maxima are listed according to the Talairach coordinate system. The clusters surviving the corrected threshold in our regions of interest are highlighted in bold. The *t* values reported in the last 2 columns were extracted from the within-group analyses for the control group and for the FEP group. The *t* value reported for the conjunction analysis corresponds to the lowest *t* value between the 2 groups. There was no region of significant differences in activation for the "FEP greater than controls" contrast.

[b] These peaks belong to the same cluster of activation.

[c] These peaks belong to the same cluster of activation.

[d] These peaks belong to the same cluster of activation.

[e] These peaks belong to the same cluster of activation.

[f] These peaks belong to the same cluster of activation.

NORMAL BRAIN ACTIVATION DURING SUCCESSFUL MEMORY FORMATION

The event-related fMRI paradigm used in the present study allowed us to contrast the pattern of brain activation elicited by successful and unsuccessful encoding trials. This contrast is regarded as ideal for brain imaging studies of episodic memory encoding because it offers a unique opportunity to isolate the pattern of brain activation related to successful encoding.[23,42] Although the subsequent recognition memory performance of the FEP group was below that of healthy controls, our conjunction analysis demonstrated several brain regions showing a similar pattern of subsequent memory effect activation in both the subjects with FEP and healthy controls. In addition, the between-group analysis for the subsequent memory contrast did not demonstrate any regions showing significantly greater activation in the control group relative to the FEP group, although a few brain regions showed greater activation for the FEP group.

Perhaps the most interesting implication of these results is that the brain regions that make memory encoding successful *can* be recruited in FEP. The brain regions that showed subsequent memory effect activation in both groups, as demonstrated by the conjunction analyses, are consistent with previous reports in studies with healthy subjects.[23-25] Some authors have suggested that the medial temporal lobe activation observed in the subsequent memory effect contrast reflects the creation of a successful memory encoding trace, promoting subsequent retrieval of the encoded information.[24,25,43] In contrast, activation in the inferior prefrontal cortex has been attributed to encoding effort, a process that is intimately linked to encoding success.[43] The fact that both the inferior prefrontal cortex and the medial temporal lobes were active in the FEP group is evidence that patients can recruit the same encoding processes that lead to optimal retrieval in healthy subjects. However, the poorer subsequent recognition performance in the FEP group relative to the control group implies that these successful encoding processes were used

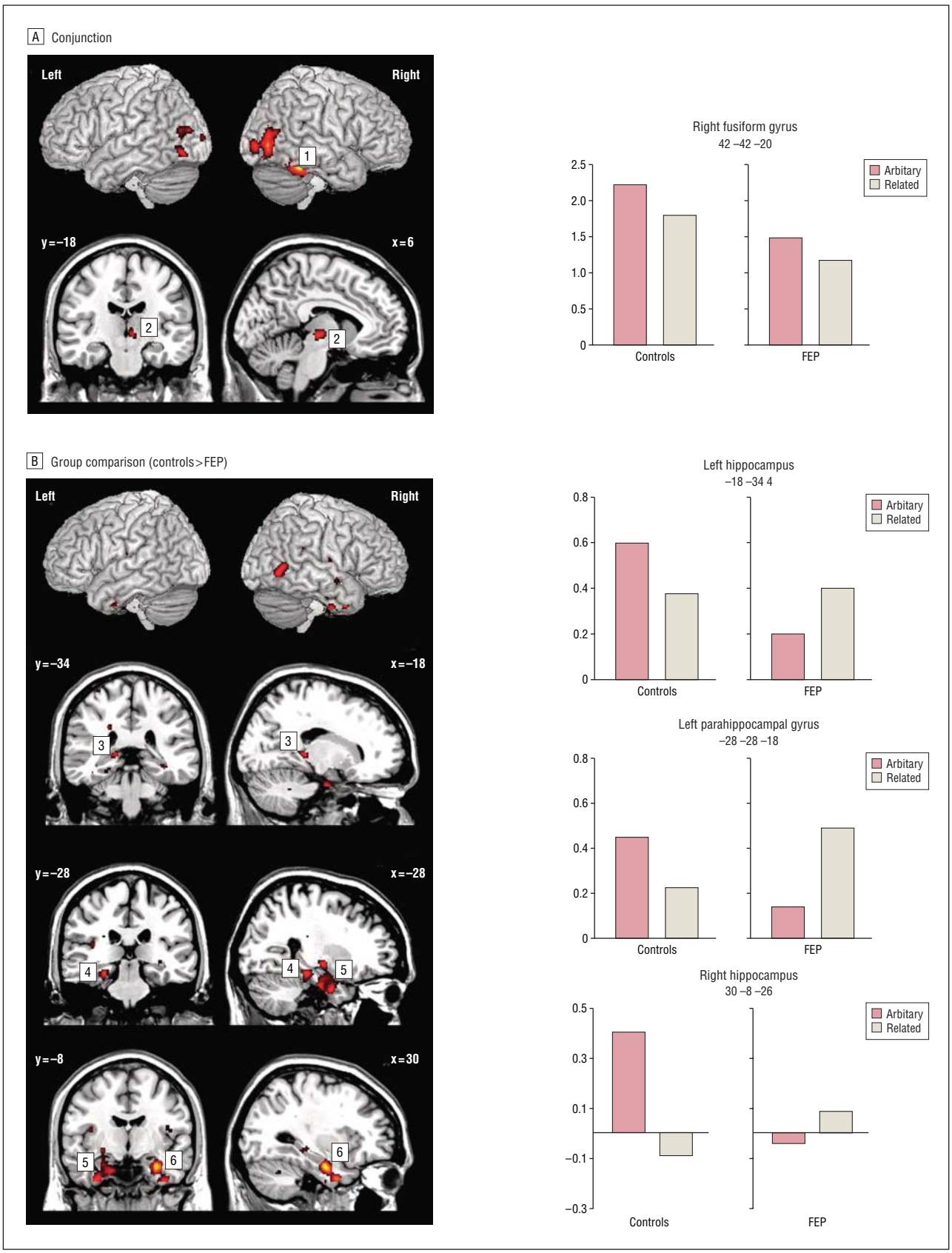

Figure 2. Results from the analyses of arbitrary pairs relative to semantically related stimulus pairs and parameter estimates of selected peaks. A, Conjunction analysis showing the regions of activation common to both groups. B, Between-group analysis showing the regions that were significantly more active in the control group relative to the first-episode psychosis (FEP) group. Insets, The insets in both parts represent the Talairach coordinates x, y, and z, that is, right to left, anterior to posterior, and superior to inferior, respectively. 1, Right fusiform gyrus; 2, thalamus/red nucleus; 3, left posterior hippocampus; 4, left parahippocampal gyrus; 5, left parahippocampal gyrus; and 6, right anterior hippocampus.

Table 6. Results of Between-Group Analysis and Conjunction Analysis for Subsequent Memory Effect Contrast[a]

Cluster Size	*t* Value	Talairach Coordinates			Hemisphere	Region	*t* Value	
		x	y	z			Controls	FEP
					FEP > Controls			
98[b]	3.85	−48	−6	40	Left	Precentral gyrus	−2.5	3.41
52	4.38	40	−2	−12	Right	Superior temporal	−4.25	2.45
32	4.07	46	−12	24	Right	Insula	−2.75	3.06
20	3.81	16	−16	−2	Right	Thalamus	−2.54	3.36
28	4.14	−2	−20	22	Left	Postcentral	−3.42	3.41
98[b]	4.55	−46	−24	38	Left	Postcentral	−4.25	2.88
19	3.92	−10	−66	18	Left	Precuneus	−3.58	2.16
					Conjunction (FEP ∩ Controls)			
96	2.94	−12	48	50	Left	Superior frontal	2.95	3.19
70	**3.00**	**−52**	**34**	**16**	**Left**	**Inferior frontal**	**3.02**	**3.03**
18	**2.61**	**−34**	**34**	**−22**	**Left**	**Inferior frontal**	**2.61**	**2.68**
10	2.05	−56	18	26	Left	Inferior frontal	3.19	2.06
339	**2.74**	**−40**	**16**	**22**	**Left**	**Inferior frontal**	**4.28**	**2.75**
150	2.24	−40	4	24	Left	Precentral	2.55	2.24
14	2.38	−26	−34	76	Left	Postcentral	2.54	2.39
144	2.95	50	36	14	Right	Middle frontal	3.26	2.96
14	**2.73**	**22**	**32**	**−20**	**Right**	**Inferior frontal**	**2.75**	**3.27**
15	**2.69**	**60**	**14**	**36**	**Right**	**Inferior/middle frontal**	**2.71**	**2.8**
40	2.42	42	12	24	Right	Inferior frontal	2.47	2.42
99	**2.87**	**−20**	**−2**	**−22**	**Left**	**Hippocampus**	**2.88**	**2.9**
3709[c]	**3.67**	**−22**	**−26**	**−10**	**Left**	**Hippocampus**	**3.67**	**3.67**
3709[c]	3.46	−26	−32	−20	Left	Parahippocampal	4.83	3.46
49	2.72	−10	−52	10	Left	Posterior cingulate	3.03	2.72
53	2.88	36	−12	−34	Right	Parahippocampal/inferior temporal	2.88	3.19
3624[d]	4.86	28	−30	−30	Right	Parahippocampal/fusiform	4.86	4.89
11	2.28	12	−36	−12	Right	Parahippocampal	2.31	2.44
51	3.09	−42	−18	−26	Left	Inferior temporal	3.16	3.09
34	3.12	−36	−8	20	Left	Insula	3.23	3.12
22	2.48	−14	−30	24	Left	Caudate tail	2.51	2.76
38	2.89	28	−30	26	Right	Insula	3.67	2.89
13	2.10	−28	−60	50	Left	Superior parietal lobule	2.1	2.11
3709[c]	5.04	−44	−74	−2	Left	Fusiform/inferior occipital	4.99	5.04
12	2.46	30	−60	16	Right	Middle temporal	2.71	2.47
3624[d]	4.22	30	−74	34	Right	Occipital	5.35	4.24

Abbreviation: FEP, first-episode psychosis.

[a] The cluster size represents the number of voxels. The x, y, and z coordinates of local maxima are listed according to the Talairach coordinate system. The clusters surviving the corrected threshold in our regions of interest are highlighted in bold. The *t* values reported in the last 2 columns were extracted from the within-group analyses for the control group and for the FEP group. The *t* value reported for the conjunction analysis corresponds to the lowest *t* value between the 2 groups. There was no region of significant differences in activation for the "Controls greater than FEP" contrast.

[b] These peaks belong to the same cluster of activation.

[c] These peaks belong to the same cluster of activation.

[d] These peaks belong to the same cluster of activation.

less often in FEP, despite the explicit encoding cues that encouraged deep processing of the image pairs.

Additionally, there were a few regions showing greater subsequent memory effect in FEP relative to healthy controls. Although the larger clusters of between-group differences in activation were located in the left precentral and postcentral regions, implicated in movement of the right side of the body, our analyses did not disclose any significant difference in the proportion of unanswered encoding trials (in which the subject did not do a mouse click during encoding) between successful and unsuccessful encoding trials between the 2 groups. Moreover, the parameter estimates suggest that there was both an increase in activation for the successful trials and a decrease in activation for the unsuccessful trials in that region. It is thus unclear at this point which processes are implicated in the greater subsequent memory effect activation observed in FEP relative to our healthy control group.

Even if the mechanisms leading to more labile recruitment of successful encoding processes in FEP are not fully understood, that these successful encoding processes *can* be recruited in FEP opens the possibility that memory performance could be improved in these individuals if they learned to use these successful encoding processes more consistently. This finding has exciting implications for devising efficient cognitive remediation strategies in FEP.

It remains unclear whether patients with longer-term schizophrenia can also activate these brain regions that support successful memory encoding. If so, then cognitive remediation therapy focusing on successful encoding could be useful at all stages of the illness. If not, then identifying when the changes happen could help us understand

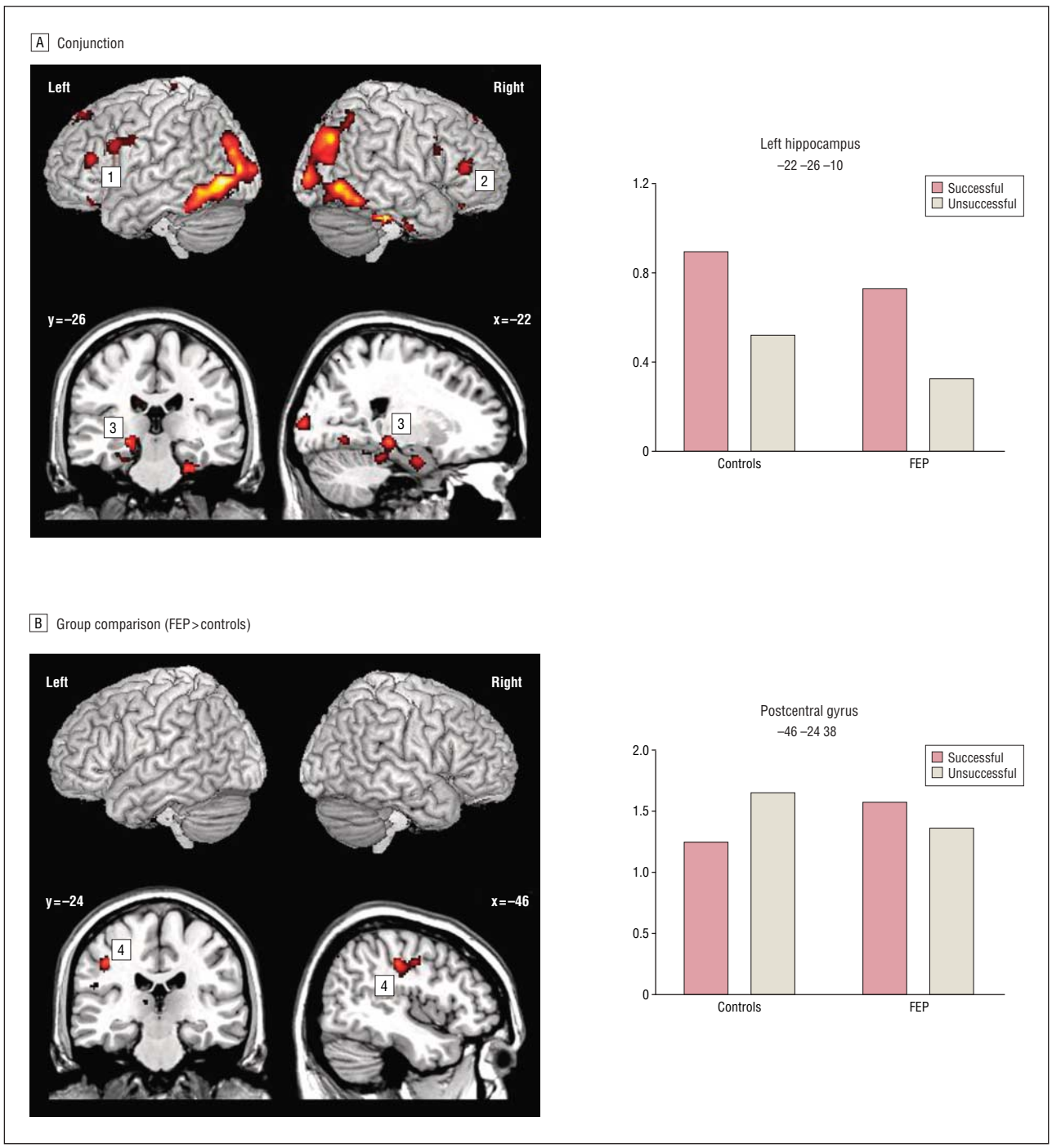

Figure 3. Results from the analyses of subsequent memory effect (ie, successful relative to unsuccessful encoding) and parameter estimates of selected peaks. A, Conjunction analysis showing the regions of activation common to both groups. B, Between-group analysis showing the regions that were significantly more active in the first-episode psychosis (FEP) group relative to the control group. Insets, The insets in both parts represent the Talairach coordinates x, y, and z, that is, right to left, anterior to posterior, and superior to inferior, respectively. 1, Left inferior prefrontal; 2, right inferior prefrontal; 3, left hippocampus; and 4, left sensorimotor cortex.

and eventually prevent the deterioration of successful memory encoding processes in schizophrenia.

RELATIVELY NORMAL ASSOCIATIVE PROCESSING

Contrary to our initial hypothesis, subjects from our FEP group were able to apply an associative encoding strategy and showed a subsequent modulation of their recognition performance as a function of encoding strategies. Indeed, the main effect of encoding strategy on the subsequent recognition test and the lack of a significant interaction between group and encoding strategy during the recognition test suggest that associative encoding promoted subsequent memory recognition to a greater extent than did deep item-oriented encoding in both

groups. This modulation of memory performance was accompanied by a normal modulation of brain activation as a function of encoding strategies. The similar pattern of activation observed for associative encoding in both groups included bilateral inferior prefrontal cortex and bilateral medial temporal areas, albeit not localized in the hippocampus.

Although neither the conjunction nor the interaction analyses showed a significant effect in the hippocampus for the contrast between associative and item-oriented encoding, activation in this region was observed in our healthy group.[60] Such a pattern of greater medial temporal activation has been repeatedly reported in healthy subjects for tasks that emphasize associative encoding relative to deep item-oriented encoding.[28,29,63] The lack of a significant conjunction or interaction in that region, however, makes it impossible to draw clear conclusions about the level of hippocampal activation in FEP during associative encoding.

Inferior prefrontal activation has mainly been observed when associative encoding is contrasted to more shallow item-oriented encoding tasks.[28] Our results suggest that, even though we tried to match the depth of our 2 encoding tasks, the associative encoding task could have resulted in deeper encoding than the item-oriented task, hence the inferior prefrontal activation observed in both groups for the contrast between associative and item-oriented encoding.

A few recent fMRI studies have used a manipulation of encoding instructions in patients with a longer history of schizophrenia.[4,64,65] These studies used a level-of-processing paradigm contrasting activation elicited by deep-semantic encoding to shallow-perceptual encoding. At least 2 of these studies[4,64] reported activation in the inferior prefrontal cortex that was common to people with schizophrenia and healthy controls. In agreement with these previous reports, our results suggest that both inferior prefrontal and medial temporal activation can be modulated in FEP as a function of encoding strategies. In addition, our results suggest that this normal modulation of brain activity as a function of encoding strategies can be observed even when the instructions promote associative encoding, and not strictly for deep item-oriented encoding. Cognitive remediation programs may be able to capitalize on associative encoding strategies to improve memory in patients with FEP. Future studies should be conducted to assess whether associative encoding instructions can also promote subsequent memory in patients with a longer history of schizophrenia.

ABNORMAL SEMANTIC RELATEDNESS PROCESSING

Contrary to what was observed for our other 2 fMRI contrasts, and in line with our hypothesis, large clusters of differences in activation between groups were observed for the contrast between arbitrary and semantically related image pairs. These clusters were located in the medial temporal lobes bilaterally, including the amygdala, hippocampus, and parahippocampal gyrus, as well as a few lateral temporal and insular regions. In these regions, the control group showed greater activation for the arbitrary pairs relative to the related pairs (ie, positive t values for the contrast between arbitrary and related pairs), whereas the FEP group showed reduced activation for the arbitrary pairs (ie, negative t values for the contrast between arbitrary and related pairs, except for 1 peak in the right inferior temporal gyrus). What makes this finding particularly striking is the fact that the medial temporal lobes otherwise exhibited normal modulation of activity in our other contrasts. Hence, this effect on medial temporal lobe activation appears to be process specific.

This pattern of between-group differences in activation observed during encoding[1] was accompanied by a similar group × semantic relatedness interaction in subsequent recognition performance, such that the FEP group showed greater recognition impairment for the arbitrary pairs relative to the related pairs. Taken together, these results suggest that a failure to engage additional medial temporal lobe–dependent relational binding when presented with arbitrary pairs during encoding could have led to the poorer subsequent recognition performance for the arbitrary pairs in the FEP group.

It is likely that for the episodic memory encoding task, the control subjects, aware of the upcoming recognition test, kept this test in mind and consequently associated the arbitrarily paired stimuli to promote subsequent retrieval of these pairs. In FEP, the lack of additional activation for the arbitrary pairs during encoding could be linked to a failure to recognize or react to incongruous pieces of information, either because of semantic relatedness disturbances and/or because they did not keep the subsequent recognition test in mind during encoding. Previous studies have suggested that being aware of such arbitrary associations, as in the transitive inference task, for example, can increase memory performance.[66] Hence, it follows that a lack of awareness of the arbitrary nature of the association may in part explain the lower performance and lack of hippocampal activation in FEP. Deficits have indeed been reported in schizophrenia for transitive inference tasks with the use of arbitrary association, but not when semantically related items are used.[67] Moreover, the deficit in the transitive inference task with arbitrary associations was accompanied by an abnormal pattern of hippocampal activation.[67]

In patients with schizophrenia, failure to use semantic relatedness information to improve episodic memory performance has also been noted in studies that use lists of items belonging to a restricted number of semantic categories. When asked to freely recall the items from these lists, patients with schizophrenia do not spontaneously use semantic clustering as a strategy to improve their memory performance.[68-73] This last example illustrates that patients with schizophrenia do not benefit from semantic relatedness to the same extent as control subjects do.

Semantic relatedness disturbances that could contribute to the failure to recognize or make use of semantic associations in schizophrenia have been reported previously in priming studies[74-76] (see Minzenberg et al[39] for a review), studies looking at clustering of responses along common dimensions during semantic fluency tasks,[77,78] and studies in which subjects are asked to make judg-

ments of proximity, congruency, or relatedness between concepts.[38,40,79,80] A previous fMRI study has also observed semantic relatedness disturbances in subjects with chronic schizophrenia.[41] Their semantic memory task required subjects to judge whether 2 words evoked a third object (eg, the pair *honey-sting*s that evokes the word *bee*). Compared with healthy controls, patients with schizophrenia had an increased tendency to find links between unrelated items, and this was accompanied by a group × condition interaction in the pattern of medial temporal lobe (including amygdala, hippocampus, and parahippocampal gyrus) activation similar to that observed in our study.

Such dysfunctions in semantic relatedness processing may be in accordance with observations of semantic relatedness disturbances in schizophrenia made more than a century ago by Kraepelin and Bleuler (cited in Spitzer[81]). These very early studies used word-association tests in which subjects were presented with a word and had to respond by saying the first word that came to their mind. Such studies contributed to the early definitions of schizophrenia by suggesting that loose, mediated, indirect, or oblique associations characterized thinking in these patients. Given our pattern of results, it seems that such semantic relatedness dysfunctions remain a key feature in the presentation of schizophrenia spectrum psychoses, even at a relatively early stage of the illness. Hence, our findings suggest that these deficits may affect not only semantics and language but memory functions as well. Considering that the study of memory can offer unique insight into the representation and organization of information in the brain, the current findings point to a fundamental difficulty in detecting and forming arbitrary associations in FEP. Given the possible links between such a deficit and the development of certain psychotic symptoms,[40,80-82] semantic relatedness dysfunctions likely represent a cognitive vulnerability marker rather than a consequence of psychosis.

LACK OF HIPPOCAMPAL VOLUME DIFFERENCES

In this study, we did not observe significant between-group differences for the left or right hippocampal volume. A recent meta-analysis by Vita et al[18] looked at hippocampal volume in FEP relative to healthy controls, and they reported effect sizes ranging from –0.06 to 1.21 (mean weighted d=0.47) in the right hippocampus and from 0.10 to 1.32 (mean weighted d=0.66) in the left hippocampus. Although our results are below the reported mean ESs, they are within the range of reported results, and it is interesting that half of the studies reviewed by Vita et al[18] also had a comparable or smaller number of subjects relative to our study. At this point, it is not clear which clinical or methodologic variables might have had a significant influence on the magnitude of the differences in hippocampal volume between people with FEP and healthy control subjects reported in different studies.

LIMITATIONS

As with all brain imaging studies, we had to rely on self-selected inclusion criteria for subject recruitment. For instance, we chose to include patients presenting with a first episode of schizophrenia-spectrum disorders, which included schizophrenia, schizoaffective disorder, and psychosis not otherwise specified and excluded affective psychosis and substance-induced psychosis. When patients with FEP are recruited, including all those who meet criteria for nonaffective psychosis is a reasonable strategy because these fall within the spectrum of schizophrenia when diagnoses are reassessed at 1 year.[83,84] In addition, there is little evidence that the diverse psychotic diagnoses are related to distinct pathophysiologic processes, especially in the early stages of illness. Although the inclusion of patients with distinct diagnoses could potentially have affected our pattern of results, the fact that we nonetheless observed selective dysfunctions argues for a deficit in semantic relatedness processing that is common to patients presenting with a FEP within the spectrum of schizophrenia diagnoses.

Another potential limitation is that we chose to include patients only once they were judged stable enough to undergo the imaging procedure and comply with the task requirements. In consequence, at the time of imaging most patients had been taking low doses of antipsychotic medication for a short time (median, 17 weeks; mean, 25 weeks). This sampling strategy, however, ensured recruitment of a larger proportion of patients presenting with a FEP than would have been possible had we limited our inclusion criteria to drug-naive patients only. Moreover, relying entirely on previously unmedicated patients could also have biased our patient sample toward patients who show fewer behavioral disturbances. In addition to antipsychotic medication, 2 of our patients were taking low doses of anticholinergic medication (mean, 1.5 mg of benztropine mesylate), but they did not seem to have difficulty with our memory task. Finally, even though patients were judged stable enough at the time of imaging, 3 of the patients who underwent imaging had to be excluded from the analyses because their behavioral performance showed that they did not comply with the instructions of the memory encoding task used for fMRI acquisition. Although the inclusion of medicated and relatively stable patients could imply that medication may have affected the cognitive processes being studied and limit the generalizability of our findings to unmedicated patients with FEP, including patients who are stable enough to comply with the imaging procedures is likely to produce more reliable results for fMRI studies of cognitive functions than by including unmedicated and symptomatic patients who are not able to follow the task instructions.

Despite our exclusion of patients who did not comply with the task instructions, we observed a main effect of group on behavioral performance during both memory encoding and memory recognition. The observation of intact patterns of hippocampal and prefrontal activation in 2 of our contrasts, however, argues against a generalized effect of task performance on the pattern of activation observed for contrasts targeting specific memory processes such as those used in the present study. Instead, between-group differences in activation were specific to the semantic relatedness contrast and were ac-

companied by a group × semantic relatedness interaction observed in the behavioral performance at the time of retrieval. It is thus unlikely that our pattern of results reflected general memory impairments. Our results, in fact, suggest a specific dysfunction of semantic relatedness encoding.

CONCLUSIONS

In a group of patients being treated for a first episode of nonaffective psychosis, the hippocampus showed abnormal activation only in response to a manipulation of semantic relatedness and not during successful memory encoding and associative processing. This argues against a general inability to recruit this brain region in people with FEP. From a clinical perspective, these findings have several implications. First, the intact processes, such as those involved in successful memory encoding, could be capitalized on to improve memory performance in patients with FEP. Because episodic memory has been shown to have a great influence on the functioning of patients with schizophrenia, improving memory performance could have a significant effect on the functional outcome of patients with FEP. Second, along with other cognitive processes that have been suggested to be at the core of psychotic experiences, difficulties in discriminating between conceptually arbitrary or related pieces of information or in binding arbitrarily paired items likely represent an important cognitive (or representational) problem that may confer greater vulnerability to psychotic disorders and would thus be interesting to examine in high-risk populations. In addition, this semantic relatedness dysfunction is likely one of the mechanisms that affects memory consistently throughout the disease process and may represent a major obstacle to a positive functional outcome unless some corrective strategies are designed.

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