ORIGINAL ARTICLE

The Neural Basis of Relational Memory Deficits in Schizophrenia

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Context: Memory deficits are common in schizophrenia. Recent studies have demonstrated that relational memory is particularly impaired.

Objective: To study the neural correlates of relational memory in schizophrenia using functional magnetic resonance imaging.

Design: Cross-sectional case-control study.

Setting: Academic medical center.

Subjects: Twenty patients with schizophrenia and 17 control subjects.

Main Outcome Measures: Behavioral performance and brain activity were assessed during the discrimination of previously seen and novel pairs of visual stimuli, which varied in the degree of relational memory load. We performed whole-brain and region-of-interest (hippocampus) analyses.

Results: Schizophrenic subjects displayed normal activation of the presupplementary motor area and ventral prefrontal cortex, but significantly decreased recruitment of the right parietal cortex and anterior cingulate cortex when discriminating novel pairs derived from a sequence of stimuli. Discrimination accuracy was decreased in schizophrenia only when the flexible representation of a sequence was required. This selective deficit was associated with decreased activation of the right parietal cortex and left hippocampus.

Conclusions: Schizophrenia is characterized by a specific deficit of relational memory, which is associated with impaired function of the parietal cortex and hippocampus. Abnormal relational memory may be at the core of 2 prominent features of schizophrenia, ie, cognitive deficits and psychosis.

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SCHIZOPHRENIA IS ASSOCIATED with deficits in several domains of cognition.[1] Memory is particularly impaired[2-6] and results in a significant decline of social functioning.[7] However, most patients with schizophrenia (hereafter referred to as schizophrenic patients or subjects) present with only subtle memory deficits on clinical examination, unlike patients with amnesia and dementia.[8] This pattern is compatible with the hypothesis that memory deficits in schizophrenia are not widespread but limited to specific domains.[6,9]

Selective deficits, associated with dysfunction in specific brain regions, would be ideal candidates to better understand the neural basis of cognition in schizophrenia. Recent behavioral studies of schizophrenic subjects have demonstrated such selective deficits for the episodic and relational forms of memory.[10-15]

Episodic memory refers to the ability to recollect events.[16] Several studies have demonstrated a selective impairment of episodic memory in schizophrenia, leaving intact the ability to remember facts.[10-13] Relational memory refers to the ability to learn associations between individual items.[17-19] One form of relational memory is transitive inference, ie, the ability to infer that A>C, knowing that A>B and B>C. In contrast to episodic memory, transitive inference can be studied in animals as well as humans, which facilitates the search for the neural basis of relational memory function.[20-22]

Titone et al[14] recently demonstrated that schizophrenic patients show a relational memory deficit during transitive inference. They trained subjects to discriminate a sequence of visual stimulus pairs (A>B, B>C, C>D, and D>E). The schizophrenic subjects were able to correctly identify the novel pairing of the 2 end items (AE), but they were significantly impaired when discriminating the novel pairing of 2 stimuli embedded within the sequence (BD). Thus, the study provided evidence that schizophrenic subjects are impaired when they have to rely on the

flexible representation of a sequence. Deficits of relational memory impair the ability to draw correct inferences based on prior learning, which may contribute to formal thought disorder and delusional thinking in schizophrenia.[23,24]

We used a recently developed functional neuroimaging paradigm[22] to study the neural basis of transitive inference in schizophrenia. We hypothesized that schizophrenic subjects would be impaired selectively during transitive inference judgments and that this deficit would be associated with a decreased activation of brain regions previously found to support transitive inference in humans.[20-22] Specifically, we hypothesized that the hippocampus, known to be crucial for transitive inference[22,25] and relational memory,[18,26] would be dysfunctional in schizophrenia.

METHODS

SUBJECTS

After approval of the study protocol by the McLean Hospital Institutional Review Board, Belmont, Mass, we obtained written consent from 17 healthy control subjects and 20 patients with schizophrenia and schizoaffective disorder recruited from an academic psychiatric hospital community. All subjects underwent a Structured Clinical Interview for *DSM-IV*, supplemented by information from treating physicians when available. Controls with significant medical, neurological, or psychiatric illness and schizophrenic patients with significant medical or neurological illness or a history of substance dependence were excluded. Two controls and 4 schizophrenic subjects were excluded from analysis because their performance accuracy in the overlapping pairs during off-line training (<66%) and during functional magnetic resonance imaging (fMRI) (<80%) did not meet our a priori criteria. One schizophrenic subject was excluded because of incomplete imaging data.

Our study group included 10 male and 5 female controls, as well as 11 male and 4 female patients with schizophrenia and schizoaffective disorder. The subject groups were matched for mean±SD age (control group, 38.1±10.3 years; schizophrenia group, 39.7±11.1 years), parental education (control group, 14.6±2.5 years; schizophrenia group, 14.4±3.0 years), and premorbid verbal IQ as estimated by the North American Adult Reading Test (NAART) score (control group, 118.3±5.2; schizophrenia group, 113.3±9.5). Thirteen patients received a diagnosis of schizophrenia and 2 patients received a diagnosis of schizoaffective disorder according to the *DSM-IV*.[27] The following mean±SD scores on clinical scales were obtained in the patient group: Positive and Negative Syndrome Scale, 57.2±9.6 (positive subscale, 13.8±3.8; negative subscale, 18.1±5.0; general subscale, 25.3±5.0)[28]; Abnormal Involuntary Movements Scale, 0.5±1.1[29]; and Beck Depression Inventory, 15.0±9.6.[30] All subjects were right-handed except for 1 left-handed male schizophrenic patient according to the Edinburgh Handedness Inventory.[31]

EXPERIMENTAL PARADIGM

We used a paradigm recently described in detail.[22] Before fMRI, subjects were trained to identify the winner in 4 nonoverlapping pairs of visual stimuli (condition P) and in 4 pairs forming a sequence of 5 stimuli (condition S) (**Figure 1** and **Table 1**). During scanning they were asked to remember the previously seen pairs or to make inferences on novel pairings, drawn from nonoverlapping pairs (condition IP) or from the sequence of overlapping items (condition IS). The experiment was designed primarily to study which brain regions were more active during transitive inferences (condition IS) compared with nontransitive inferences (condition IP). In addition, the design allowed us to contrast novel pairs that differed in the number of items with an ambiguous reinforcement history as follows: (1) no ambiguous item (ie, a previous winner plus a previous loser; all pairs in condition IP); (2) 1 item with ambiguous (50% winner) reinforcement history (all pairs in condition IS except for BD); and (3) 2 items with ambiguous reinforcement history (the BD pair) (Figure 1 and Table 1).

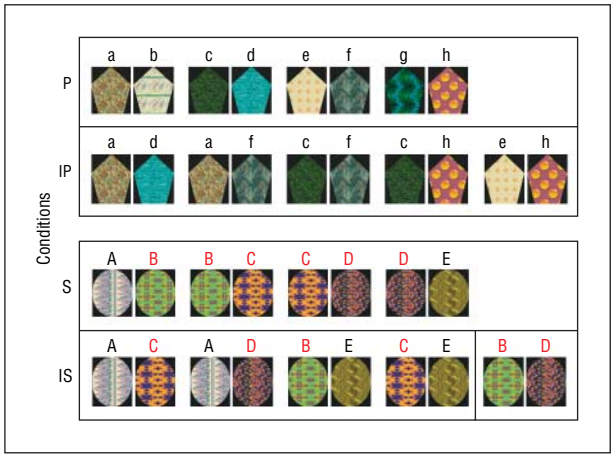

Figure 1. Stimulus set and task conditions. Before functional magnetic resonance imaging (fMRI), subjects were trained to discriminate nonoverlapping pairs (condition P) and an overlapping sequence of pairs (condition S). The reinforced item within each pair is shown on the left. Items highlighted with red were reinforced in one pairing and not reinforced in the other. During fMRI, subjects were asked to recollect the correct response for previously seen pairs and to infer the correct response for novel pairings of items. For novel pairs drawn from the nonoverlapping stimulus set (condition IP), each item was previously reinforced or nonreinforced but not both (ambiguity score, 0). Novel pairings drawn from the overlapping sequence of pairs (condition IS) contained 1 or 2 items with ambiguous reinforcement history (ambiguity score 1 and 2, respectively). No letters were shown in the experiment, and the presentation of the pairs and the position of the 2 stimuli within each pair were randomized.

Table 1. Stimulus Sets for fMRI*

Stimulus Set	Stimulus Pairs	No. of Ambiguous Items
Previously seen		
P	a>b, c>d, e>f, g>h	
S	A>B, B>C, C>D, D>E	
Novel		
IP	a>d, a>f, c>f, c>h, e>h	0
IS	A>C, A>D, B>E, C>E	1
	B>D	2

Abbreviation: fMRI, functional magnetic resonance imaging.
*The 4 conditions of P, IP, S, and IS are described in the "Experimental Paradigm" subsection of the "Methods" section.

STIMULI

Two sets of pattern fills (8 for the nonoverlapping pairs and 5 for the overlapping pairs) were randomly assigned to pairs of pentagonal and ellipsoid shapes for each participant, and the positions of the pattern fills were rotated across subjects.

TRAINING BEFORE SCANNING

Identical to a previously published procedure from our group,[22] participants were shown pairs of visual items on a computer screen and asked to indicate by button push which "hid" a smiling face. The left/right position of individual patterns for each pair was counterbalanced. A correct guess during training revealed the smiling face under the visual pattern, and an incorrect guess moved the selected visual pattern but the smiling face did not appear. Participants were trained first on nonoverlapping pairs (a-h; Table 1), then on the sequence of overlapping pairs (A-E; Table 1). For each condition, there were 3 training blocks, consisting of 60, 60, and 24 trials. Participants saw an equal number of each of the pairs in the overlapping and nonoverlapping stimulus sets during training. After completion of the training blocks, participants were tested on a mixture of overlapping and nonoverlapping pairs in a single block of 48 trials containing 6 instances of each of the 8 stimulus pairs. Subjects who did not perform to our criterion of 66% correct for each stimulus pair (7 controls and 9 schizophrenic subjects) received an additional training block of 24 trials of the kind they failed (overlapping pairs in all cases). These subjects were then retested with the same 48-trial mixed block before proceeding to fMRI.

TASK DURING fMRI

All subjects participated in two 5-minute fMRI scans. Each fMRI started and ended with 30-second fixation trials. In between, 8 blocks of trials were presented in the order of P, IP, S, IS, P, IP, S, and IS or S, IS, P, IP, S, IS, P, and IP. In each block, 10 trials were presented for 3 seconds each, resulting in a total of 8 presentations for each of the 5 novel pairs of the IP and IS conditions. For each trial, subjects were instructed to indicate by button press which item they thought would be associated with a smiling face on the basis of previous experience; the smiling face was not presented.

FUNCTIONAL MRI

Subjects lay on the padded bed of a 3-T scanner (Siemens AG, Munich, Germany) in a dimly illuminated room. Foam padding was used to stabilize the head. Stimuli were generated using Presentation software (Neurobehavioral Systems Inc, Albany, Calif) on a personal computer. Images were projected onto a screen and viewed by the subjects via a tilted mirror placed in front of their eyes. After acquisition of high-resolution anatomical images for each subject, fMRI began with an initial sagittal localizer scan. The 2 fMRI scans lasted 5 minutes 5 seconds each. The first 5 seconds of each series was discarded to allow T1 signal equilibration. This was followed by collection of 120 blood oxygenation level–dependent (BOLD) functional brain images (echo time, 30 milliseconds; repetition time, 2500 milliseconds; 35 coronal sections [5 mm thick] perpendicular to the anterior commissure–posterior commissure line, starting anteriorly at the frontal pole, no skip; voxel size, $3.1 \times 3.1 \times 5$ mm; field of view, 200 mm; flip angle, 90°).

We acquired 2 types of images to assess signal distortion due to susceptibility artifacts in the BOLD images. First, an anatomical image matched to the functional BOLD images was acquired.[32] These anatomical images were acquired using the standard head coil in the coronal plane with multishot spin-echo echoplanar imaging (echo time, 80 milliseconds; repetition time, 3000 milliseconds; 1 image per section; matrix, 256×256 with 4 averages; field of view, 200 mm; 3-mm section thickness with no skip). These are susceptible to the same distortions as BOLD images are and were used to outline hippocampal regions of interest (ROIs) that could be overlaid on functional images. The second set of special-purpose images were field maps, which characterize field inhomogeneities that cause distortions of functional images.[33]

DATA ANALYSIS

Behavioral Data

Accuracy and response latency were analyzed using a repeated-measures 2 (sequence) $\times$ 2 (inference) analysis of variance (ANOVA) with diagnosis as the between-subjects factor. The IS condition was further analyzed as BD and non-BD pairs, using a 2 (diagnosis) $\times$ 2 (stimulus pair) ANOVA.

Structural Neuroimaging Data

We used a previously described morphometric protocol[34] to calculate hippocampal volume in high-resolution anatomical images with the 3-dimensional Slicer program (http://www.slicer.org). Volumes were analyzed using repeated-measures 2 (hemisphere) $\times$ 2 (region) ANOVA with diagnosis as the between-subjects factor.

Functional Neuroimaging Data

Analysis was performed using FEAT (fMRI Expert Analysis Tool), version 5.1, part of the Oxford Centre for Functional Magnetic Resonance Imaging of the Brain (FMRIB) software library (www.fmrib.ox.ac.uk/fsl). Higher-level analysis was performed using FLAME (FMRIB Local Analysis of Mixed Effects).[35] Functional data were corrected for head motion, transformed to MNI (Montreal Neurological Institute) template space, and smoothed using a 3-dimensional 8-mm full-width/half-maximum gaussian kernel to allow application of the gaussian random field theory for statistical analysis. Functional images were analyzed in 3 stages in a mixed-effects model. During the first stage, fixed-effects analysis was used. A design matrix was created for each subject that included the effects of the 5 conditions (P, IP, S, IS, and fixation baseline) and the first 2 principal components of motion parameters to explain the time course of BOLD signal change at each voxel. Motion parameters were included to account for BOLD signal changes related to head motion. The 5 effects of interest were modeled as blocks with a boxcar function convolved with 2 gamma functions. The general linear model was used to obtain parameter estimates corresponding to the magnitude of the BOLD signal response for each block type. The contrast used to study brain activation specifically related to transitive inference was $(IS - S) - (IP - P)$.[22]

In addition to this block design approach, we also performed an event-related analysis focusing on BOLD signal changes related to the BD pairs (Table 1). In this analysis, the design matrix included the effects of 6 trial types (P, IP, S, IS [BD], IS [non-BD], and fixation baseline) with a trial duration of 3 seconds (the duration of stimulus presentation). For each subject, 8 BD presentations (ie, 4 per run) interspersed throughout the IS condition, as well as 32 other IS (non-BD) pairs and 40 each of the P, IP, and S pairs (in blocks of 10 trials), were modeled. The 8 BD trials were in positions $3 + 10$, $3 + 5$, $4 + 9$, and $4 + 9$ of the 4 IS blocks. Trial-related BOLD signal change was assessed by convolving a vector of the onset times of the stimuli with a double gamma hemodynamic response function. The general linear model was used to obtain parameter estimates corresponding to the magnitude of the BOLD signal response to each trial type. In both cases, statistical parametric maps were constructed using linear contrasts of parameter estimates for the effects of interest. The

contrast used to study brain activation during BD trials was (*IS*[BD] – *IS*[non-BD]).

At a second-level analysis, the effects of runs 1 and 2 were modeled for controls and schizophrenic subjects. At a third-level analysis, individual contrast images were entered into a random-effects analysis. One- and 2-sample unpaired *t* tests were used to test for the main effects and interactions of within- and between-group effects.[36] For the whole-brain analysis, we masked the group-wise contrast images with the activation image from the first group to ensure that the findings represented true activations in that group (eg, control>schizophrenia group contrast was masked with activations in the control group). Activations within the previously defined network of brain regions supporting transitive inference judgments[22] were considered significant at a voxel extent threshold of 5 or more voxels, with $P \leq .001$, uncorrected for multiple comparisons.

Given our strong a priori hypothesis of hippocampal abnormalities during transitive inference in schizophrenia, we used 2 ROI approaches to study hippocampal activation. First, we delineated left and right anterior and posterior hippocampal volumes on the mean structural image of all study subjects and limited the whole-brain contrast image analysis to the hippocampus using these 4 masks. Activations were considered significant at $P \leq .05$, corrected for multiple comparisons within the hippocampal ROIs. Second, to confirm any significant activation within the 4 hippocampal ROIs, we outlined hippocampal regions on echoplanar-matched anatomical images. These images, representing the same degree of distortion,[37] provided high-fidelity registration with the BOLD images and allowed us to define the hippocampus along anatomical landmarks. After delineation, we coregistered the ROIs and the EP-matched anatomical images and calculated mean time courses across the ROI for individual subjects. We then extracted epochs of activity in response to a presentation of BD pairs scaled as percentage of signal change from the onset of the BD trials, and compared patterns of change across the 2 groups.

RESULTS

BEHAVIORAL DATA

Accuracy

Both groups were less accurate when recognizing novel pairs (main effect of inference, $F_{1,28}=16.33$ [$P<.001$]; nonsignificant inference × diagnosis interaction, $F_{1,28}=1.20$ [$P=.28$]) or pairs taken from the sequence (main effect of sequence, $F_{1,28}=20.90$ [$P<.001$]; nonsignificant interaction of sequence × diagnosis, $F_{1,28}=0.18$ [$P=.67$]) (**Table 2**). This indicates normal transitive inference performance in schizophrenia when all trials are analyzed together.

However, the 2 groups differed in their ability to correctly evaluate the novel-pair BD, which combines 2 stimuli rewarded equally often (50%) during training (Table 1 and Figure 1). Control subjects achieved similar accuracy for the BD pair and the remaining IS pairs ($F_{1,14}=1.21$ [$P=.29$]), whereas schizophrenic subjects were selectively impaired on the BD pairs but not the remaining IS pairs ($F_{1,14}=7.93$ [$P=.01$]) (Table 2 and **Figure 2**). A repeated-measures ANOVA revealed that this diagnosis × stimulus pair interaction approached significance ($F_{1,28}=3.63$ [$P=.07$]), consistent with a specific deficit of schizophrenic subjects on the BD pairs.

Table 2. Behavioral Data*

	Study Group, Mean ± SD	
	Control	Schizophrenia
Accuracy, %		
P	98 ± 3	96 ± 10
IP	96 ± 5	90 ± 20
S	87 ± 15	83 ± 13
IS	79 ± 16	70 ± 25
IS (non-BD)	80 ± 16	79 ± 23
IS (BD)	73 ± 24	48 ± 41
Response latency, ms		
All trials		
P	1043.4 ± 122.4	1189.8 ± 316.9
IP	1098.0 ± 274.9	1126.4 ± 304.6
S	1374.2 ± 150.0	1513.9 ± 231.1
IS	1524.3 ± 214.1	1449.7 ± 210.4
Correct trials only		
P	1025.1 ± 141.0	1104.6 ± 205.4
IP	1134.6 ± 262.5	1073.6 ± 259.4
S	1354.5 ± 166.8	1455.9 ± 145.4
IS	1517.7 ± 257.1	1547.4 ± 258.9

*The 4 conditions of P, IP, S, and IS are described in the "Experimental Paradigm" subsection of the "Methods" section.

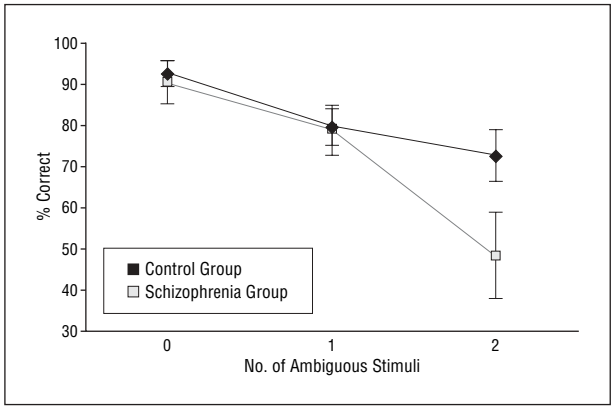

Figure 2. Accuracy for 3 different inference tasks. Accuracy was highest when both stimuli in novel pairings had an unambiguous reinforcement history (condition IP; ambiguity score, 0) and lowest when both stimuli could only be inferred from their position within the sequence (BD; ambiguity score, 2). The schizophrenia group showed a selective deficit in the BD transitive inference pairs. Error bars represent SEM.

Response Latency

Subjects needed more time to identify the pairs taken from the sequence (main effect of sequence, $F_{1,28}=73.12$ [$P<.001$]; nonsignificant diagnosis × sequence interaction, $F_{1,28}=0.44$ [$P=.51$]) (Table 2). Control but not schizophrenic subjects needed more time to identify the previously rewarded stimulus in novel pairs (nonsignificant main effect of inference, $F_{1,28}=0.48$ [$P=.49$]; diagnosis × inference interaction, $F_{1,28}=8.98$ [$P=.006$]) (Table 2). This interaction was weaker if only the response latencies for correct responses were considered ($F_{1,28}=4.35$ [$P=.046$]), because schizophrenic subjects tended to respond faster when the IS trials were identified incorrectly (mean±SD, 1547.4±258.9 milliseconds

Table 3. Brain Activations During Transitive Inference Condition*

Brain Region by Hemisphere	Control Group			Schizophrenia Group			Control vs Schizophrenia Groups		
	No. of Voxels per Cluster	*z* Score†	MNI	No. of Voxels per Cluster	*z* Score†	MNI	No. of Voxels per Cluster	*z* Score†	MNI
Inferior parietal cortex (BA 40/7)									
Right	26	3.44	20, –66, 42				12	3.4	36, –60, 46
Left	214	4.08	–38, –58, 34						
Inferior frontal gyrus (BA 47)									
Right	207	4.08	36, 14, –6	184	3.96	32, 40, –16			
Left	106	4.28	–56, 34, –14						
Pre-SMA, bilateral	‡	4.39	4, 26, 56	7	3.24	0, 4, 70			
Premotor cortex (BA 6)									
Right	33	3.44	52, 18 2						
Left	95	3.8	–30, 20, 56						
Pulvinar, bilateral	§	4.39	–6, –28, 6						
Anterior cingulate cortex (BA 24/32), bilateral	163	4.73	0, 4, 28				5	3.25	–10, 18, 38
Posterior temporal cortex (BA 21/37)									
Right	67	3.71	54, –38, –16	84	4.04	64, –12, –22			
Left				59	3.63	–58, –8, –4			
Hippocampus/entorhinal cortex									
Right	283	4.22	32, –22, –28						
Left	115	3.88	–38, –24, –22						

Abbreviations: BA, Brodmann area; MNI, the MNI stereotactic space, an approximation of Talairach space[38]; pre-SMA, presupplementary motor area.
*Indicates (IS>S)>(IP>P), described in the "Experimental Paradigm" subsection of the "Methods" section. Blank cells indicate that there were no significant activations in those brain areas in that group.
†Indicates maximum *z* score.
‡The pre-SMA activation was a local maximum within a larger medial dorsal frontal activation.
§The pulvinar activation was a local maximum within a larger activation including the basal ganglia.

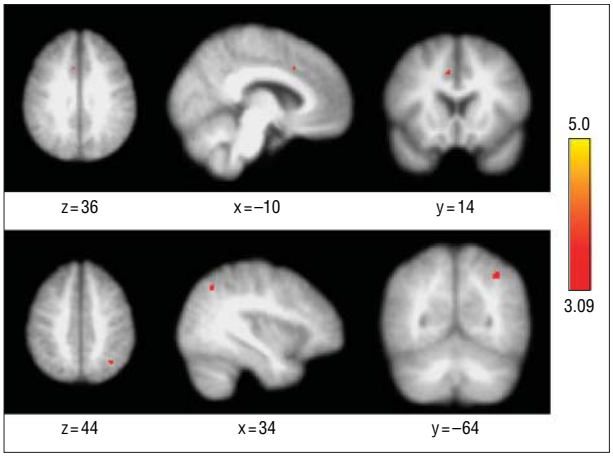

Figure 3. Magnetic resonance imaging shows abnormal brain activity in schizophrenia during transitive inference. Brain areas show significantly greater activity in healthy control subjects than in schizophrenic patients during the transitive inference condition. Both loci were mapped onto axial, parasagittal, and coronal slices from the mean structural image of the 30 study subjects ($P<.001$, uncorrected). Color bar indicates *z* scores.

for correct and 1219.8±245.9 milliseconds for incorrect trials) ($t=2.19$; [2-tailed $P=.04$]).

Neither group showed a significant relationship between NAART scores and accuracy or reaction times during the P, IP, S, or IS blocks (not shown) or during BD trials specifically ($r=0.22$ [$P=.46$] and $r=0.44$ [$P=.12$], respectively).

MRI DATA

Volumetric Data

Mean±SD hippocampal volume for left anterior, left posterior, right anterior, and right posterior regions did not differ between the control (1407±269, 1307±231, 1514±193, and 1355±250 mm^3, respectively) and the schizophrenia (1352±327, 1364±134, 1497±213, 1396±222 mm^3, respectively) groups (main effect of diagnosis, $F_{1,28}=0.01$ [$P=.91$]; diagnosis × hemisphere interaction, $F_{1,28}=0.06$ [$P=.81$]; diagnosis × anterior/posterior region interaction, $F_{1,28}=0.54$ [$P=.47$]; diagnosis × hemisphere × region interaction, $F_{1,28}=0.31$ [$P=.58$]).

fMRI Data

We explored the neural basis of transitive inference in control and schizophrenic subjects with the following 2 types of analyses: (1) all transitive inference trials compared with all nontransitive inference trials, and (2) the 8 BD transitive inference trials compared with the 32 non-BD transitive inference trials.

Transitive Inference

Consistent with our previously identified transitive inference network, control subjects showed significantly greater activation in the bilateral parietal cortex,

Table 4. Brain Activations During Hard Transitive Inference Condition*

Brain Region by Hemisphere	Control Group			Schizophrenia Group			Control vs Schizophrenia Groups		
	No. of Voxels per Cluster	*z* Score†	MNI	No. of Voxels per Cluster	*z* Score†	MNI	No. of Voxels per Cluster	*z* Score†	MNI
Inferior parietal cortex (BA 40/7)									
Right	220	4.26	32, –48, 52	16	3.41	22, –40, 66	6	3.1	28, –50, 52
Left	27	3.42	–30, –58, 62						
Inferior frontal gyrus (BA 47)									
Right				24	3.37	36, 14, 0			
Left				45	3.75	–34, 30, –8			
Premotor cortex (BA 6)				71	4.12	44, 4, 40			

Abbreviations: BA, Brodmann area; MNI, the MNI stereotactic space, an approximation of Talairach space.[38]

*Indicates BD>non-BD, described in the "Experimental Paradigm" subsection of the "Methods" section. Brain regions that are part of the transitive interference network where no significant activation was found are not shown. Blank cells indicate that there were no significant activations in those brain areas in that group.

†Indicates maximum *z* score.

premotor cortex, presupplementary motor area (pre-SMA), bilateral ventral prefrontal cortex, bilateral posterior temporal cortex, pulvinar, and right hippocampus and entorhinal cortex (**Table 3**). In contrast, schizophrenic patients showed significantly greater activation in only 3 brain regions: the pre-SMA, ventral prefrontal, and posterior temporal cortex (Table 3). A direct comparison of the 2 groups revealed significantly decreased activation during transitive inference judgments in schizophrenia in the right parietal cortex and anterior cingulate cortex (Table 3 and **Figure 3**). Parameter estimates extracted from these 2 regions were not correlated with delusional thinking, conceptual disorganization, or total Positive and Negative Syndrome Scale scores. The hippocampal ROI analysis did not reveal any significant differences between the 2 groups. All of these analyses were confirmed when using BOLD images that were corrected for field inhomogeneity–induced distortions.

BD Trials

To explore the neural basis of the selective deficit for BD pairs in schizophrenia, we studied whether brain activation differed between the BD trials and the remaining non-BD transitive inference trials. In the whole-brain analysis, we found that only the bilateral parietal cortex was more significantly activated during BD trials in controls (**Table 4**). In schizophrenic subjects, we found activation in several frontal cortical areas (Table 4). A direct comparison of the 2 groups revealed greater right parietal cortex activation in healthy controls (Table 4 and **Figure 4**A).

The ROI analysis of the 4 hippocampal regions revealed significantly stronger activation of the left anterior hippocampus in the control group (33 voxels; coordinates of peak activation at –14, –10, and –24; $z=2.59$ [$P<.05$, corrected for multiple comparisons]) (Figure 4B). Parameter estimates for this differentially activated region showed increased activation in the control group and decreased activation in the schizophrenia group during BD trials (Figure 4C); these estimates were not correlated with delusional thinking, conceptual disorganization, or total Positive and Negative Syndrome Scale scores. This difference in left anterior hippocampal activation was confirmed in a second analysis, which revealed that the control group showed a blood flow increase in response to BD trials, whereas the schizophrenia group did not (Figure 4D).

COMMENT

We have identified the neural correlates of a selective relational memory deficit in schizophrenia. Subjects with schizophrenia were able to draw correct transitive inferences about novel stimulus pairs if at least 1 stimulus had an unambiguous reinforcement history. However, they were impaired if reward contingencies were ambiguous and the flexible representation of a sequence was required for discrimination. This confirms and extends a previous study of relational memory in schizophrenia.[14] In addition, our data provide novel evidence that this relational memory deficit in schizophrenia is associated with impaired function of the right parietal cortex and medial temporal lobe (MTL).

TRANSITIVE INFERENCE NETWORK IN CONTROL AND SCHIZOPHRENIA GROUPS

In this study, we replicate a previous finding[22] that a network of brain areas (including the pre-SMA, bilateral parietal cortex, prefrontal cortex, and hippocampus) is associated with transitive inference in healthy controls. We now show normal activation of 2 nodes (ie, pre-SMA and ventral prefrontal cortex) and decreased activation of 2 other nodes (ie, right parietal and anterior cingulate cortices) within this network during transitive inference in schizophrenia.

Activation of the pre-SMA is an integral feature of transitive inference tasks.[21,22] This is in line with previous studies suggesting that the pre-SMA is involved in the control of motor sequences[39] and that this region is activated during sequence learning.[40,41] Previous stud-

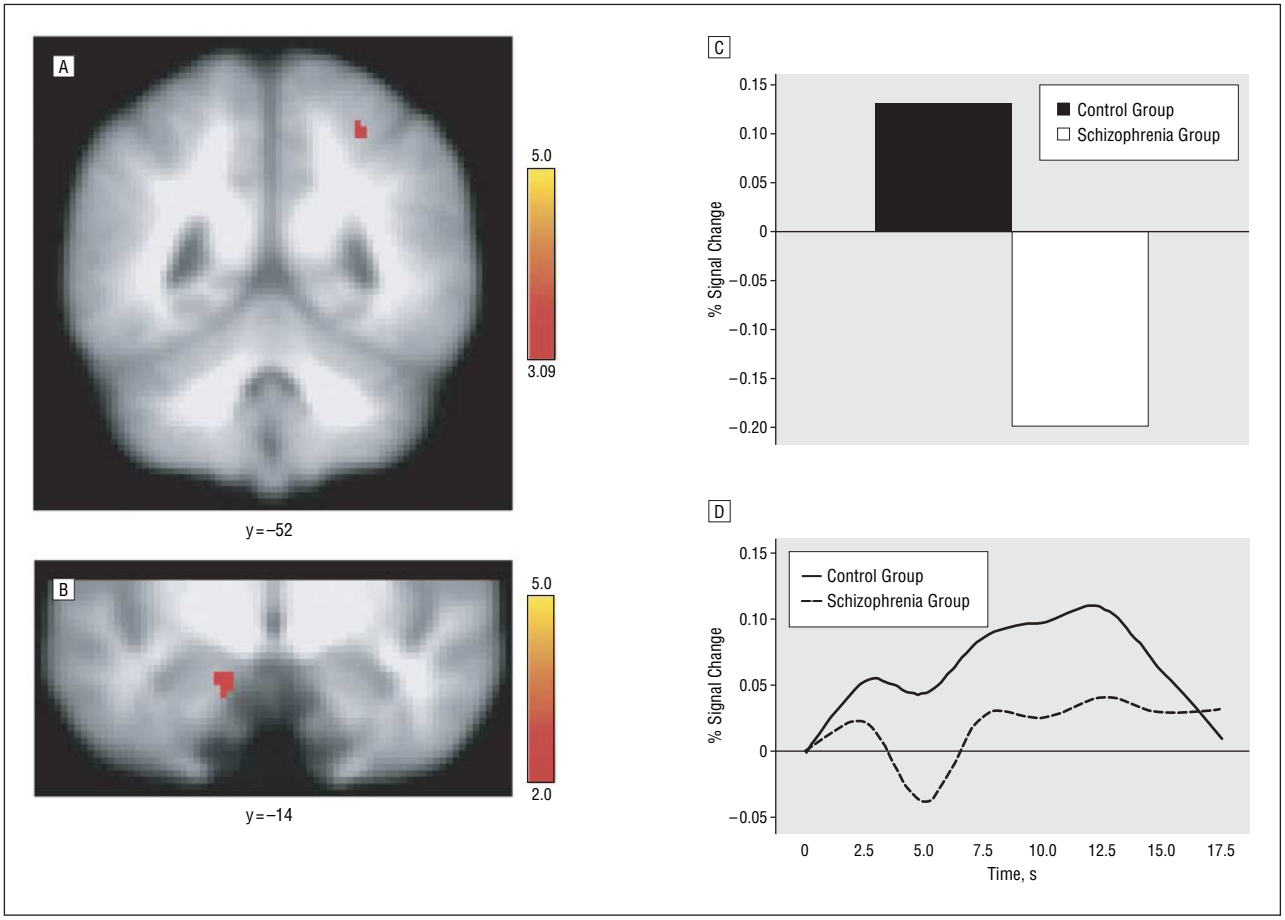

Figure 4. Abnormal brain activity in schizophrenia during trials when both stimuli could only be inferred from their position within the sequence (BD trials). A, The right parietal cortex showed significantly greater activity in healthy control subjects than in schizophrenic patients during BD trials, mapped onto a coronal slice from the mean structural image of the 30 study subjects ($P<.001$, uncorrected). B, Significantly greater activation in healthy controls than in schizophrenic patients in the left anterior hippocampus during BD trials, mapped onto a coronal slice from the mean structural image of the 30 study subjects ($P<.05$, corrected). C, Parameter estimates extracted from the differentially activated left anterior hippocampal cluster (in part B). Signal increase in controls and signal decrease in schizophrenic patients were seen during BD trials. D, Group-averaged time series of blood oxygenation–level dependent signal for the anatomically defined left anterior hippocampal region of interest during BD trials. Signal change is plotted relative to the presentation of the BD pair (time point, 0). Color bars in A and B indicate *z* scores.

ies in schizophrenia showed robust pre-SMA activation during cognitive task performance in schizophrenia.[42,43] Our results indicate that the function of the pre-SMA is also not impaired in schizophrenia during relational memory tasks that require the storage and retrieval of a sequence.

The parietal cortex (Brodmann areas 40 and 7) also appears to be a crucial node within the transitive inference network. Activation of this area during transitive inference in humans was reported by 2 previous neuroimaging studies of healthy volunteers.[21,22] It is likely that the storage of a flexible representation of visual stimuli, necessary to correctly discriminate transitive inference trials, requires access to the parietal cortex. This is supported by the demonstration of strong reciprocal connections between the parietal and prefrontal cortices and the MTL, including the entorhinal cortex and presubiculum.[44,45] A proposed role of the parietal cortex for the storage of flexible representations of stimuli is in line with recent neuroimaging studies that have demonstrated parietal cortex activation during judgments of semantic distance while comparing numbers[46] and during judgments of analogy.[47] In addition, 2 aspects of transitive inference, ie, attention and decision making, have been linked closely to the parietal cortex.[48,49]

Herein we report reduced recruitment of parietal cortex in schizophrenia during transitive inference judgments in general and during BD trials in particular. This pattern indicates abnormal parietal cortex function in schizophrenia not only during trials in which performance is significantly impaired (ie, BD), but also when performance is not significantly different. This is consistent with a fundamental parietal cortex deficit in schizophrenia.[50] Previous studies have demonstrated that abnormalities of attention, working memory, decision making, and motor control in schizophrenia are related to dysfunction of a parietal-prefrontal network.[51-55] Furthermore, the first-rank symptom of passivity or "made" experiences and the core features of catatonia (stupor and mutism) have been associated with abnormal activity of the parietal cortex.[56-58] These results have led some to suggest an important role of the parietal cortex for the cognitive deficits and psychotic features of schizophrenia, especially in "representationally guided behaviors."[50] Our data support such notions and link the abnormal pattern of parietal cortex activation to impaired relational memory in schizophrenia.

ABNORMALITIES IN THE MTL

Two lines of evidence compelled us to examine MTL function during transitive inference. First, transitive inference requires an intact hippocampal formation in animals[18,25] and is associated with hippocampal activation in humans.[18,20,22] Second, a large body of literature indicates that significant structural and functional abnormalities exist in the MTL in schizophrenia[59] and that memory deficits have been associated with abnormal recruitment of the hippocampus in neuroimaging studies.[60-65]

We found that subjects with schizophrenia were impaired in recruiting the left hippocampus during BD trials, linking deficits in relational memory to abnormal hippocampal function. This provides compelling evidence that impaired hippocampal function contributes to memory deficits in schizophrenia. It remains to be seen how region-specific abnormalities of interneurons[66] and excitatory synaptic neurotransmission[67] in the hippocampus of schizophrenia subjects are related to the deficits of relational memory reported herein. Animal models of relational memory are ideally situated to test the hypothesis of impaired hippocampal inhibition in schizophrenia.[68] Aberrant afferent signals from the association cortex, including the parietal cortex,[44] may contribute to the abnormal hippocampal signaling in schizophrenia.

LIMITATIONS

As in all neuroimaging studies of schizophrenia, our patient group was self-selected. They were stable, treated outpatients, able and willing to tolerate a training session in a challenging paradigm, followed by fMRI. Although this limits the generalizability of our findings, the study of medicated, stable outpatients has been proposed as ideal for the exploration of cognitive deficits and their treatment in schizophrenic patients.[69] The relatively high premorbid IQ of our subjects, as estimated by the NAART, is not typical for the population of schizophrenic patients at large,[70] but the lack of a relationship between NAART scores and performance indicates that this did not bias our results. Finally, although the finding of normal hippocampal volume in our patient group is in contrast to the findings of many other studies,[71] it avoids the confound of volume differences in the analysis of hippocampal activation patterns.

The experiment included a total of 8 BD and 32 non-BD IS trials per subject. Furthermore, stimulus onset asynchrony was fixed at 3 seconds and not jittered. Both of these factors likely limited our power to detect differences in the event-related analysis of BD trials. The fact that we still found significant group differences highlights their robust nature. It would be desirable to test the neural basis of transitive inference with a design that includes 6 stimuli (A-F), allowing for 3 BD-like pairs of stimuli (B>D, B>E, and C>E). However, preliminary data from this experimental paradigm in young healthy controls indicate that schizophrenic subjects would unlikely be able to achieve accuracy sufficient for a valid neuroimaging experiment.

Our study was performed using a 3-T MRI scanner, where distortions and loss of the BOLD signal in the temporal and frontal lobes are significant. We confirmed our findings in the medial temporal lobe with unwarped functional images and with an ROI analysis that used anatomical images matched for the degree of distortion. However, it is possible that the power to detect group differences in brain activation varies between regions and that the parietal cortex yielded an underlying pathology more readily than did the hippocampus.

IMPLICATIONS

In this study, subjects needed to access the mental representation of a sequence to infer relationships between items in novel configurations. Recent accounts of transitive inference link the cerebral cortex to the storage of stimulus representations and the hippocampus to the access of these representations to make inferences about the relationships between items.[18] We have found reduced activity in the anterior cingulate cortex, right parietal cortex, and hippocampus in schizophrenia during transitive inference judgments. Thus, we conclude that patients with schizophrenia are impaired at multiple levels, including storage of stimulus representations (in the parietal cortex), flexible retrieval and comparison of stimuli (in the hippocampus), and error monitoring and attention (in the anterior cingulate cortex[72]). However, hippocampal abnormalities made a unique impact on performance because schizophrenic patients were behaviorally impaired only when flexible access to sequentially arranged stimuli was needed (the BD condition).

Because relational memory deficits can lead to inferential thinking abnormalities, including a "jump-to-conclusions" cognitive style, they may be related to the delusions and thought disorder of schizophrenia.[23,24,73] Thus, an impaired ability to retrieve a flexible representation of prior experience might be at the core of 2 prominent features of schizophrenia, ie, memory deficits and psychosis. This is not a simple relationship, however, as there was no correlation between brain activation and the degree of psychosis in our patient group. Relational memory deficits may contribute to the formation of delusions but might not be linked to the degree of delusions at the time of study. In the future, it would be helpful to compare schizophrenic patients with and without delusions with the transitive inference task.

Studying the neural basis of cognitive deficits in schizophrenia promises to uncover new treatment targets.[74] The selective relational memory deficit described herein is attractive because animal models of transitive inference are well established[25,75] and recent studies have demonstrated a transitive inference network in humans,[20-22] providing the opportunity to study treatment effects in several species. Given the abnormalities in multiple brain areas during transitive inference in schizophrenia, we speculate that investigation of this neuroimaging phenotype and genes implicated in neural development and neurotransmission, such as neuregulin 1, may prove fruitful.

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Correction

Errors in Text. In the Original Article by Birmaher et al titled "Clinical Course of Children and Adolescents With Bipolar Spectrum Disorders," published in the February issue of the ARCHIVES (2006;63:175-183), errors occurred in the text on pages 176 and 179. On page 176, in the "Methods" section, "Subjects" subsection, fifth paragraph, the third sentence should have read as follows: "Subjects with BP-II had the onset of their mood disorders significantly later and had significantly lower rates of comorbid attention-deficit/hyperactivity disorder than subjects with BP-I and BP-NOS ($P \leq .05$)." On page 179, under "Weekly Mood Symptomatic Status by BP Subtype," first paragraph, the second sentence should have read as follows: "Within the syndromal symptoms, subjects with BP-I spent significantly more weeks with syndromal mania and mixed symptoms than those with BP-NOS, and subjects with BP-II spent significantly more time with depressive symptoms than those with BP-I and BP-NOS (all comparisons, $P \leq .001$)."