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Functional magnetic resonance imaging of internal source monitoring in schizophrenia: Recognition with and without recollection

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Abstract

Patients with schizophrenia tend to have impaired source monitoring and intact item recognition, suggesting an over-reliance of familiarity effects. We previously demonstrated that providing patients with a levels-of-processing (LOP) semantic encoding strategy normalized source monitoring. The current blood-oxygen-level-dependent (BOLD) functional magnetic resonance imaging (fMRI) study tests the hypothesis that patients will have abnormally increased fronto-temporal activation despite intact performance. fMRI was measured in 13 patients and 13 demographically matched healthy controls during a LOP source monitoring paradigm. SPM2 was used for standard pre-processing and statistical analyses, with a corrected significance threshold of $p < .05$. Examination of accuracy and speed measures did not reveal any group differences in task performance. Regardless of source retrieval success both groups activated expected prefrontal and parietal regions, with no areas of relatively greater control versus patient activation. In support of the hypothesis, patients showed abnormally increased activation in temporolimbic areas including middle and superior temporal gyrus, thalamus, and parahippocampal gyrus. Activation in these areas was associated with worse positive and negative symptoms, but did not correlate with performance, suggesting inefficient rather than compensatory activation.

Keywords: Schizophrenia; Episodic memory; Functional magnetic resonance imaging; Source memory

1. Introduction

During memory retrieval individuals can recognize an item as previously presented based either on a sense of familiarity or on recollection of the encoding event. This distinction is relevant to schizophrenia given evidence of patient over-reliance on familiarity effects (Danion et al., 1999), which contributes to relatively mild recognition versus recall deficits (Aleman et al., 1999). This phenomenon can be demonstrated with the "remember"/"know" paradigm (Huron et al., 1995; Tulving, 1985) in which patients have increased rates of "know" responses (i.e., familiarity based recognition) and decreased rates of "remember" responses (i.e., recognition with recollection of the encoding event).

Source monitoring (Johnson et al., 1993) provides a way to assess episodic retrieval without the meta-cognitive demand of a "remember"/"know" procedure. During source monitoring participants are required to recognize "old" items and identify the context in which they were presented. For successful monitoring to occur it is necessary that contextual information is related and successfully bound as part of the memory trace (Chalfonte and

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Johnson, 1996). Because relational binding of contextual information is a central problem in schizophrenia (Waters et al., 2004), it is not surprising that patients have impaired source monitoring even when recognition is intact (Vinogradov et al., 1997; Danion et al., 1999). Patients with prominent hallucinations and thought disorder also tend to misattribute internal items to external sources (Keefe et al., 2002).

The levels-of-processing paradigm (LOP; Craik and Lockhart, 1972) is an ideal framework for source monitoring studies because it provides encoding contexts that control for patient impairments in strategic memory processes (Iddon et al., 1998; Stone et al., 1998). LOP tasks control for patients' failure to spontaneously organize words semantically (Koh and Peterson, 1978; Paulsen et al., 1995; Iddon et al., 1998) by requiring alternation between "shallow" orthographic encoding and "deep" semantic encoding. This results in faster and more accurate recognition of deeply processed words, suggesting that semantic processing is sufficiently intact in schizophrenia for patients to benefit from organizational strategies (Ragland et al., 2003). To assess LOP effects on source monitoring subjects are required to recollect the encoding context ("shallow"/"deep" judgment) when a word is recognized. We investigated this behaviorally using a two-high threshold multinomial modeling procedure (Batchelder and Riefer, 1990; Bayen et al., 1996), and did not find any group differences (Ragland et al., 2006), further emphasizing the importance of encoding strategy. However, only controls had a significant LOP effect on source monitoring, suggesting that relational binding of semantic information was not fully normalized in schizophrenia.

The purpose of the current study is to use functional magnetic resonance imaging (fMRI) to determine whether unimpaired source monitoring is accompanied by normal patterns of brain activation in schizophrenia. Although we are not aware of any previous fMRI studies of source monitoring in schizophrenia, there have been fMRI studies of LOP effects on word encoding, recognition, and word-stem completion (Bonner-Jackson et al., 2005; Heckers et al., 1998; Ragland et al., 2005; Weiss et al., 2003). These have generally found poorly modulated frontotemporal activation in patients during deep versus shallow processing, with evidence of both abnormally increased and decreased activation in prefrontal cortex and temporolimbic brain regions. As in our previous studies of encoding and recognition (Ragland et al., 2001, 2004, 2005) we hypothesize that patients will show a pattern of abnormally increased activation in prefrontal and temporolimbic regions. Controls are predicted to demonstrate the more focal pattern of left prefrontal, superior parietal, and precuneus activation found in previous source monitoring studies of normal cognition (Dobbins et al., 2002; Kahn et al., 2004; Lundstorm et al., 2005; Mitchell et al., 2004; Rugg et al., 1999).

2. Methods

2.1. Subjects

Participants were from a sample of 14 patients with schizophrenia (2 female) and 14 healthy comparison subjects (1 female) that completed a previous LOP word encoding and recognition study (Ragland et al., 2005). The current sample of 13 patients and 13 controls excluded one male control with excessive motion (i.e., greater than 4 mm translation in x, y, or z dimension), and one male patient who did not complete source monitoring. Groups did not differ on age (control mean age=31.1, SD=6.7; patient mean age=35.2, SD=8.2 years), education (control mean level=14.1, SD=1.9; patient mean level=13.5, SD=2.8 years), parental education (control mean level=14.5, SD=2.6; patient mean level=13.4, SD=3.0 years), or reading level (NART) (Nelson, 1982) (control mean NART=31.8, SD=6.4; patient mean NART=28.5, SD=7.4 years). All controls and all but one patient were right-handed.

Participants underwent standardized assessment procedures, consisting of medical, neurological, psychiatric, neurocognitive evaluations, and laboratory tests. The psychiatric evaluation for patients included clinical assessment, structured interview (First et al., 1996a,b), history obtained from family, care providers, and records, and scales for measuring symptoms administered by investigators trained to a criterion reliability of 0.90, intraclass correlation. All patients were 18–45 years old and had a DSM-IV diagnosis of schizophrenia established in a consensus conference based on all information available. Patients were excluded for other psyhiatric Axis I disorders including substance related disorders (DSM-IV and laboratory data including toxicology); previous electroconvulsive therapy; history of any neurologic event or disease; medical diseases affecting brain function or interfering with participation including hypertension (BP>140/90), cardiac disease, diabetes mellitus, endocrine disorders, renal disease, chronic obstructive pulmonary disease, orthopedic circumstances and metallic inserts interfering with MR scanning; pregnancy determined by a serum test; not proficient in English; mental retardation (i.e., full scale IQ<70); and learning disorders. Patients were mildly to moderately ill according to Scales for Assessment of Negative Symptoms (SANS) (Andreasen, 1983) (mean score=25.4, SD=15.6, range=2–62),

Scales for Assessment of Positive Symptoms (SAPS) (Andreasen, 1984) (mean score=18.1, SD=13.4, range=0–48) and Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham, 1980) (mean score=30.5, SD=8.0, range=18–43). All patients were medicated with antipychotics (2 first generation, 10 second generation, 1 combined), with average daily dose of 386.7 mg/day in chlorpromazine equivalents (SD=196, range=160–500) and 18.4 mg/day in olanzapine equivalents (SD=10.7, range=5.0–45.0). No patient was receiving anticholinergics or other psychotropic medication. Mean age of onset was 20.6 years (SD=3.1), and duration was 14.6 years (SD=9.4). Control subjects underwent the same evaluation procedures (First et al., 1996a,b), and met above exclusion criteria including any history of illness affecting brain function or any major psychiatric illness in first-degree relatives. After complete description of the study written informed consent was obtained.

2.2. Test procedures

A source monitoring task was administered as the final run of a previously described LOP word encoding and recognition paradigm (Ragland et al., 2005). During encoding participants were presented with 80 target words (40 shallow, 40 deep). During shallow encoding a left button press was made if the word was in uppercase letters, and a right button for lowercase letters. During deep encoding a left button press was made if the word was concrete, and a right button if abstract. During source monitoring 40 target words (20 shallow, 20 deep) were presented with 20 novel words at a presentation rate of 3 s each with a variable inter-stimulus-interval (ISI) ranging from 5 to 13 s. Participants were instructed to press a left button if it was an "old" word presented during shallow encoding, a middle button if it was an "old" word presented during deep encoding, and a right button if it was a "new" word. Task administration was triggered by the scanner and coupled to image acquisition using the PowerLaboratory® platform (Chute and Westall, 1997). All subjects correctly completed practice trials before imaging to ensure comprehension and familiarity with the response apparatus.

2.3. Image acquisition

Data were acquired on a clinically approved 3T Siemens Trio Scanner. A 5-minute magnetization-prepared, rapid acquisition gradient echo image (MPRAGE) was acquired for anatomic overlays of functional data and spatial normalization (Talairach and Tournoux, 1988). fMRI was acquired with blood oxygenation level dependent imaging (BOLD) (Bandettini et al., 1992) using a 36 slice whole-brain, single-shot gradient-echo (GE) echo-planar (EPI) sequence (TR/TE=3000/30 ms, FOV=240 mm, matrix=64×64, slice thickness/gap=3/0 mm).

Table 1
Performance during source monitoring in patients with schizophrenia versus comparison subjects

Performance measure	Comparison						
	Patients (N=13)		Subjects (N=13)		F (df=1,24)	p	d[a]
	M	SD	M	SD			
Foil words							
True Negative[b]	12.61	4.79	15.00	2.89	2.37	0.14	−0.60
False Positive[c]	7.38	4.79	5.00	2.89	2.37	0.14	0.60
True Negative Reaction Time[d]	1490.90	250.00	1417.05	247.50	0.07	0.79	0.29
False Positive Reaction Time	1843.22	397.82	1785.59	372.19	0.13	0.72	0.15
Target words							
True Positive, Incorrect Source[e]	9.46	3.20	7.15	2.23	1.80	0.19	0.84
True Positive, Correct Source[f]	14.54	5.35	17.23	4.87	1.80	0.19	−0.52
False Negative[g] Total	16.00	5.93	15.61	5.45	0.03	0.86	0.07
True Positive, Incorrect Source Reaction Time	1843.56	301.33	1798.25	147.37	0.01	0.91	0.19
True Positive, Correct Source Reaction Time	1747.62	222.80	1800.89	237.02	1.20	0.28	−0.23
False Negative Reaction Time	1653.93	340.03	1596.98	264.69	0.11	0.74	0.19

[a] d=effect size (Cohen, 1988).
[b] True Negative=foil words correctly recognized as "new".
[c] False Positive=foil words incorrectly identified as "old".
[d] Reaction Time in milliseconds.
[e] True Positive, Incorrect Source=target words correctly recognized as "old" with a source misattribution error.
[f] True Positive, Correct Source=target words correctly recognized as "old" with correct source identification.
[g] False Negative=target words incorrectly identified as "new".

2.4. Data analysis

Accuracy and speed (median reaction time) measures were obtained separately for targets and foils (Table 1). For foils, scores were calculated for words correctly recognized as "new" (True Negative), and incorrectly identified as "old" (False Positive). For targets, scores were calculated for correctly recognized "old" words with incorrect source identification (True Positive, Incorrect Source), words recognized as "old" with correct source identification (True Positive, Correct Source), and words incorrectly identified as "new" (False Negative). One-way analysis of variance (ANOVA) tested for group performance differences, with the significance threshold set at $p < .05$ (two-tailed). Previously performed multinomial analysis was not applicable as it generates group-level parameters that cannot be utilized in event-related fMRI.

fMRI data were preprocessed in SPM2 (Wellcome Department of Cognitive Neurology, London, UK) using standard procedures. Images were slice-timed and motion-corrected to the median image using trilinear interpolation. Translational and rotational motion parameters did not differ between groups [$F(1,24) = 2.89$, $p = .10$]. The structural image was coregistered to the median image, and spatial normalization parameters of the structural image to a standard T1 template were applied to all functional images. Finally, the images were spatially smoothed (8 mm FWHM, isotropic) and high-pass filtered (0.008 Hz).

Subject-level statistical analyses were performed using the general linear model in SPM2. Condition events were modeled for each stimulus presentation using a canonical hemodynamic response function. For source monitoring, there were 5 event types: true positive, incorrect source; true positive, correct source; true negative; and response errors (false negative and false positive). Contrast maps were obtained through linear contrasts of event types.

Group-level random effects analyses were performed in SPM2 for within- and between-group comparisons. Within-group analyses were accomplished by entering whole brain contrasts for controls and patients separately into one-sample *t*-tests. Between-group analyses were accomplished by entering whole brain contrasts for controls and patients into two-sample *t*-tests, and inclusive masks restricted voxels with above-threshold activation from the within-group contrasts. Simple regression analyses were performed in SPM2 to examine correlations between task related activation and performance (number

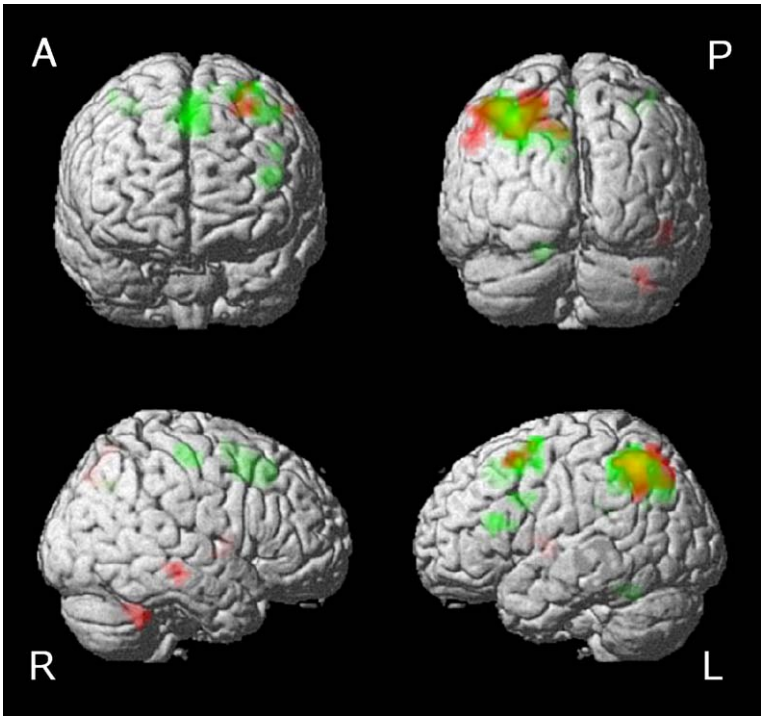

Fig. 1. Blood-oxygen-level-dependent fMRI signal change during true positive, incorrect source minus true negative responses. Statistical parametric maps are surface-rendered on smoothed brain images to illustrate activation in patients (red color) and controls (green color). Overlapping activation is illustrated in yellow. Colored areas indicate a difference in signal change that exceeds a threshold corresponding to a corrected *p*-value of 0.05. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

correct) in patients and controls, and correlations with symptoms (total SANS and SAPS scores) in patients. Significance thresholds for all SPM2 analyses were based on spatial extent (k) and peak height (u). We used a height threshold corresponding to a p-value of 0.005 requiring a minimum of 8 voxels in a cluster.

3. Results

3.1. Performance

As can be seen in Table 1, there were no group differences in accuracy or reaction time for any performance measure. This parallels results from previous multinomial analyses (Ragland et al., 2006) that controlled for potential interactions between guessing, source monitoring, and recognition parameters. Because of the relatively small sample sizes observed effect sizes (d; Cohen, 1988) were also calculated. Effect sizes of .20 are considered small, .50 medium, and .80 or greater are large. As illustrated in Table 1, effect sizes for all reaction time measures were small, suggesting that even with a large sample there would have been no group differences. However, true negative and false positive variables had medium effect sizes, suggesting that a larger sample of patients may have had significantly higher rates of false positive errors and lower rates of true negative responses. There was also a medium effect size for true positive, correct source responses, and a large effect for true positive, incorrect source responses. With larger samples it is possible that patients would have had an increased rate of true positive responses in which the source was incorrect, and a reduced rate of true positive responses in which the source was correct.

3.2. fMRI results

As in previous studies (e.g., Dobbins et al., 2002) true negative responses were used as a reference condition because correctly identifying foils as "new" could be accomplished based on familiarity, with little or no reliance on source memory or associated control processes. Subsequent contrasts examined task related activation when words were correctly recognized with and without successful recollection of the encoding source.

3.2.1. Recognition without recollection

This first analysis contrasted the reference condition with task related activation when individuals correctly recognized target words as "old", but made a source misattribution error. As can be seen in Fig. 1 and Table 2, controls had extensive left frontal activation including

Table 2
Local cluster-level maxima of blood-oxygen-level-dependent fMRI signal change during true positive, incorrect source minus true negative responses in healthy comparison subjects and patients with schizophrenia

Group and region	Estimated			Coordinates[a]		
	Brodmann's area	Size[b]	z-score[c]	x	y	z
Comparison subjects ($n=13$)						
Left inferior frontal gyrus	9	8	3.05	−45	9	29
Left inferior frontal gyrus	45	19	3.81	−45	22	17
Left middle frontal gyrus	6	9	3.83	−38	13	43
Left middle frontal gyrus	6	*	3.58	−22	7	55
Right precentral gyrus	4	14	3.82	30	−16	49
Left anterior cingulate gyrus	32	121	4.52	−4	21	43
Left posterior cingulate gyrus	31	8	3.25	−4	−36	27
Left inferior parietal lobule	7, 40	215	4.96	−34	−52	47
Left cerebellum	–	12	3.14	−15	−44	−15
Patients ($n=13$)						
Left middle frontal gyrus	8	18	4.17	−30	17	47
Left thalamus	–	11	2.93	−11	0	7
Right thalamus	–	8	3.5	11	−8	0
Right superior temporal gyrus	21	15	3.6	49	−26	−5
Left superior parietal lobule	7, 40	140	3.68	−26	−64	44
Patients > comparison subjects						
Right superior temporal gyrus	21	45	4.6	49	−26	−5

[a] Coordinates from the stereotaxic atlas of Talairach and Tournoux (1988).
[b] Size = number of above-threshold activated voxels, * indicates a sub-region of a larger cluster.
[c] Peak activation in a cluster of at least eight voxels in which the difference in signal change exceeded an extent and threshold corrected p-value of 0.05.

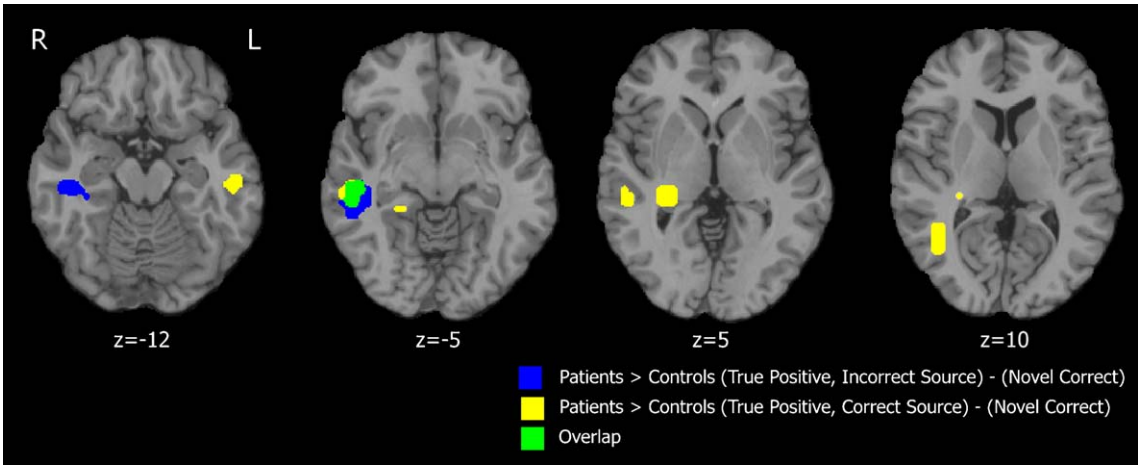

Fig. 2. Increased patient versus control blood-oxygen-level-dependent fMRI signal change during true positive, incorrect source and true positive, correct source minus true negative responses. Statistical parametric maps are surface-rendered on transaxial brain slices (radiologic convention) to illustrate patient overactivation during true positive, incorrect source (blue color) and true positive, correct source (yellow color). Overlapping activation is illustrated in green. Thresholding as in Fig. 1. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

dorsolateral prefrontal cortex [DLPFC; Brodmann Area (BA) 9], Broca's area (BA 45), and pre-motor cortex (BA 6). Additional left hemisphere activation was seen in the anterior (BA 32) and posterior cingulate (BA 31), inferior parietal cortex (BA 7, 40), and cerebellum. Activation was also seen in the right pre-central gyrus (BA 4). Patients activated left prefrontal (BA 8) and parietal cortex (BA 7, 40), and showed additional effects in bilateral thalamus and right superior temporal gyrus (BA 21). Between group contrasts did not reveal any

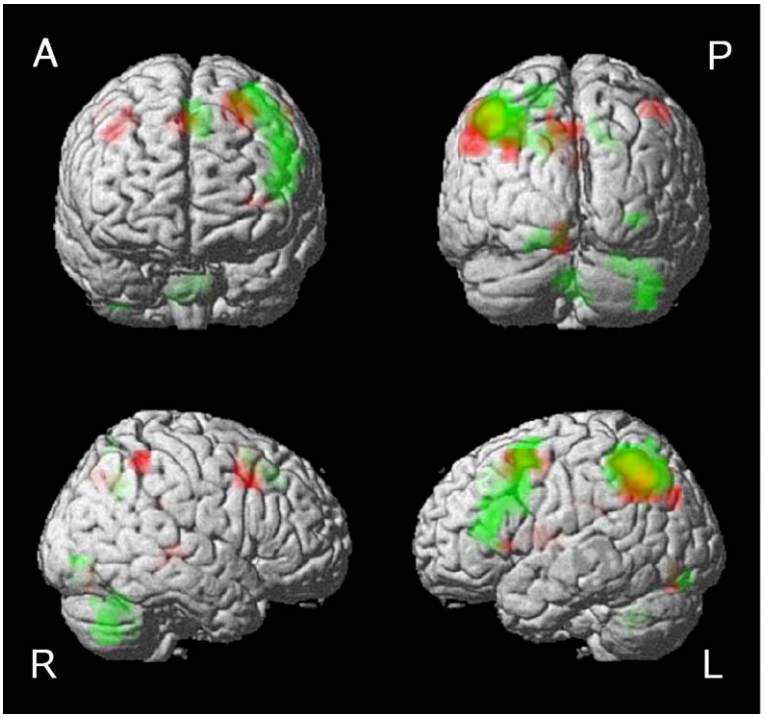

Fig. 3. Blood-oxygen-level-dependent fMRI .signal change during true positive, correct source minus true negative responses. Statistical parametric maps are surface-rendered, color coded, and thresholded as in Fig. 1.

areas of relatively greater control activation. However, patients had abnormally increased activation in the right superior temporal gyrus (BA 21; Fig. 2). This provides partial support for the hypothesis that patients would show fronto-temporal overactivation.

Regression analyses did not reveal any performance correlations. In patients, positive symptoms were correlated with increased activation in the left precuneus (BA 19; $x=-22$, $y=-82$, $z=36$; z-score=3.67), and negative symptoms with reduced activation in the left inferior parietal lobule (BA 40; $x=-38$, $y=-48$, $z=46$; z-score=3.17).

3.2.2. Recognition with recollection

This second analysis contrasted the reference condition with fMRI signal when individuals correctly recognized target words as "old" and correctly identified the source of the encoding event. Results are illustrated in Fig. 3 and Table 3. Controls again relied on a large number of left prefrontal regions including DLPFC (BA 9), Broca's area (BA 45), and pre-motor and supplementary motor cortices (BA 6, 8). They showed left inferior and superior parietal activation (BA 7, 40), and also activated the right precuneus (BA 31), bilateral visual association cortices (BA 17, 18, 19), and bilateral cerebellum. Patients also

Table 3
Local cluster-level maxima of blood-oxygen-level-dependent fMRI signal change during true positive, correct source minus true negative responses in healthy comparison subjects and patients with schizophrenia

Group and region	Estimated			Coordinates[a]		
	Brodmann's area	Size[b]	z-score[c]	x	y	z
Comparison subjects ($n=13$)						
Left inferior frontal gyrus	9	*	3.56	−55	12	25
Left inferior frontal gyrus	45	*	3.73	−51	26	21
Left middle frontal gyrus	6	191	4.16	−34	11	55
Left medial frontal gyrus	6, 8	47	3.58	−4	24	43
Left inferior parietal lobule	7, 40	269	4.86	−41	−52	54
Left superior parietal lobule	7	*	3.04	−15	−59	62
Right precuneus	31	14	3.57	19	−56	36
Left inferior occipital gyrus	17, 18, 19	15	2.82	−15	−88	−6
Right middle occipital gyrus	18	8	3.32	30	−80	1
Left cerebellum	–	31	3.54	−4	−52	−28
Right cerebellum	–	74	3.53	41	−64	−34
Patients ($n=13$)						
Left middle frontal gyrus	6	*	3.3	−30	17	47
Left medial frontal gyrus	6	70	3.4	−19	2	48
Right precentral gyrus	9	23	3.6	41	20	36
Left insula	13	8	3.05	−34	19	3
Right anterior cingulate gyrus	32	34	3.88	8	21	43
Posterior cingulate gyrus	23	37	3.71	0	−32	27
Left thalamus	–	32	3.36	−11	0	7
Right thalamus	–	21	3.16	26	−25	1
Right parahippocampal gyrus	30	*	2.9	22	−37	−2
Left precuneus	7	48	3.7	−8	−60	40
Left precuneus	19	18	3.4	−34	−75	37
Left inferior parietal lobule	40	123	4.32	−45	−56	43
Right inferior parietal lobule	40	19	3.25	45	−41	50
Left lingual gyrus	18	12	3.14	−8	−77	−13
Patients > comparison subjects						
Right thalamus	–		3.62	30	−29	5
Right parahippocampal gyrus	36	23	2.67	22	−37	−5
Left middle temporal gyrus	21	13	3.23	−51	−19	−12
Right middle temporal gyrus	21	13	3.92	51	−26	−5
Right superior temporal gyrus	39	*	2.98	41	−58	10

[a] Coordinates from the stereotaxic atlas of Talairach and Tournoux (1988).
[b] Size=number of above-threshold activated voxels, * indicates a sub-region of a larger cluster.
[c] Peak activation in a cluster of at least eight voxels in which the difference in signal change exceeded an extent and threshold corrected p-value of 0.05.

activated left (BA 6) and right (BA 9) frontal lobe areas, as well as left inferior parietal cortex (BA 40). As in the previous contrast, patients had additional activation in the bilateral thalamus, and also showed effects in the left insula, anterior and posterior cingulate (BA 32, 23), right anterior parahippocampal gyrus, left precuneus (BA 7, 19), right inferior parietal cortex (BA 40), and left lingual gyrus (BA 18). Between-group contrasts failed to find any areas of relatively greater control versus patient activation. However, patients had abnormally increased temporolimbic activation (Fig. 2), including right anterior parahippocampal gyrus extending into the right thalamus, bilateral middle temporal gyrus (BA 21) and right superior temporal gyrus (BA 39). Hypothesized patient overactivation was again restricted to temporal rather than frontal regions.

Regression analyses did not reveal any associations with performance in patients. In controls better performance was correlated with increased activation in the left anterior cingulate gyrus (BA 24; $x=0$, $y=4$, $z=44$; z-score=3.70) and left superior parietal lobule (BA 7, 40; $x=-34$, $y=-52$, $z=60$; z-score=3.44). In patients positive symptoms were associated with increased right DLPFC (BA 9; $x=49$, $y=15$, $z=28$; z-score=3.07) and middle occipital activation (BA 37; $x=41$, -71, 0; z-score=3.53). More severe negative symptoms correlated with increased left posterior cingulate gyrus activation (BA 31; $x=-15$, $y=-53$, $z=28$; z-score=4.09); increased right hemispheric activation in the VLPFC (BA 47; $x=38$, $y=21$, $z=-8$; z-score=3.08) precentral gyrus (BA 9; $x=38$, $y=13$, $z=40$; z-score=3.43), inferior temporal gyrus (BA 37; $x=41$, $y=-66$, $z=-4$; z-score=4.01), middle temporal gyrus (BA 19; $x=38$, $y=-61$, $z=14$; z-score=4.21; BA 39; $x=49$, $y=-58$, $z=10$; z-score=2.84; BA 22; $x=51$, $y=-40$, $z=-1$; z-score=3.18), superior temporal gyrus (BA 39; $x=49$, $y=-57$, $z=25$; z-score=3.69), parahippocampal gyrus (BA 37; $x=34$, $y=-44$, $z=-8$; z-score=3.52; BA 30; $x=19$, $y=-37$, $z=-5$; z-score=3.48), and supramarginal gyrus (BA 40; $x=55$, $y=-42$, $z=35$; z-score=3.73); and increased bilateral precuneus activation (BA 19; $x=-34$, $y=-78$, $z=33$; z-score=3.32; BA 7; $x=30$, $y=-52$, $z=50$; z-score=3.32).

3.2.3. Source recollection

This final contrast compared fMRI response when words were recognized with correct source identification versus recognition without source identification. As can be seen in Fig. 4 (Table 4), controls showed expected patterns of left frontal and parietal activation, with effects seen in dorsolateral (BA 46) and ventrolateral (BA 44) prefrontal cortex, and left superior parietal cortex (BA 7,

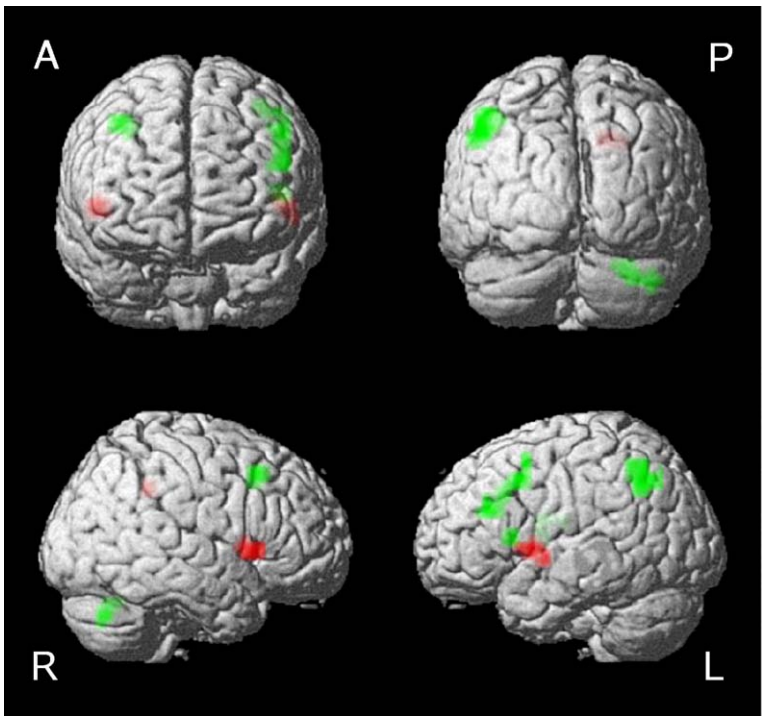

Fig. 4. Blood-oxygen-level-dependent fMRI signal change during true positive, correct source minus true positive, incorrect source responses. Statistical parametric maps are surface-rendered, color coded, and thresholded as in Fig. 1.

Table 4
Local cluster-level maxima of blood-oxygen-level-dependent fMRI signal change during true positive, correct source minus true positive, incorrect source in healthy comparison subjects and patients with schizophrenia

Group and region	Estimated			Coordinates[a]		
	Brodmann's area	Size[b]	z-score[c]	x	y	z
Comparison subjects (N = 13)						
Left inferior frontal gyrus	44	8	2.88	−45	15	10
Left middle frontal gyrus	8	36	3.43	−49	13	40
Left middle frontal gyrus	46	*	3.43	−45	30	21
Left middle frontal gyrus	6	*	2.78	−38	10	51
Right middle frontal gyrus	8	16	3.32	38	21	43
Left caudate	–	16	2.98	−11	−3	19
Left superior parietal lobule	7, 40	38	3.35	−41	−56	50
Right cerebellum	–	25	3.44	26	−63	−20
Patients (n = 13)						
Right inferior frontal gyrus	45	19	3.42	49	11	3
Left insula	13	20	2.94	−49	4	3
Right posterior cingulate gyrus	31	10	3.36	19	−42	39
Left superior temporal gyrus	22	20	2.89	−55	−4	−3

[a] Coordinates from the stereotaxic atlas of Talairach and Tournoux (1988).
[b] Size = number of above-threshold activated voxels, * indicates a sub-region of a larger cluster.
[c] Peak activation in a cluster of at least eight voxels in which the difference in signal change exceeded an extent and threshold corrected *p*-value of 0.05.

40). Controls also activated bilateral pre-motor regions (BA 6, 8), left caudate, and right cerebellum. Prefrontal activation in patients was restricted to the right hemisphere (BA 45). Patients also activated the left insula (BA 13), right posterior cingulate (BA 31), and left superior temporal gyrus (BA 22). There was no evidence of group differences when between-group contrasts were performed.

4. Discussion

When patients with schizophrenia and healthy volunteers attempted to retrieve the source of successfully recognized words they showed robust activation in prefrontal and parietal episodic memory areas, and did not differ in task performance speed or accuracy. Consistent with fMRI studies of source monitoring (Dobbins et al., 2002; Kahn et al., 2004; Lundstorm et al., 2005; Mitchell et al., 2004; Rugg et al., 1999), both groups activated prefrontal, superior parietal, and precuneus regions regardless of source retrieval success. As in our previous LOP study of word encoding and recognition (Ragland et al., 2005), patients did not show any areas of abnormally decreased activation. In partial support of our original hypothesis, patients did show abnormally increased activation in temporolimbic areas. However, frontal lobe activity was not abnormally increased contrary to this initial prediction. These results, together with findings of unimpaired recognition (Kubicki et al., 2003; Ragland et al., 2003, 2005) and source monitoring (Ragland et al., 2006) during LOP paradigms, points to the central importance of semantic encoding strategies in schizophrenia. When these strategies are provided, patients can successfully recruit prefrontal resources and improve familiarity based recognition and autonoetic source retrieval. However, abnormally increased activation in temporolimbic areas suggests residual differences in retrieval networks.

Abnormally increased temporolimbic activation occurred in right superior temporal gyrus during retrieval attempt, and right superior and middle temporal gyrus, right anterior parahippocampal gyrus and thalamus, and left middle temporal gyrus during retrieval success. The two neocortical temporal lobe regions are components of a heteromodal association cortex involved in language and multimodal sensory integration, known to be disrupted in schizophrenia (Pearlson et al., 1996). The superior temporal gyrus (STG) has received the most attention given consistent gray matter volume reductions in schizophrenia (Shenton et al., 2001). STG overactivation has also been seen during verbal fluency tasks (Frith et al., 1995; Yurgelun-Todd et al., 1996; Fletcher et al., 1996), and negatively correlated with presence of hallucinations and thought disorder (Kircher et al., 2001; McGuire et al., 1998). The middle temporal gyrus has been associated with language and semantic memory processing in healthy subjects (Tranel et al., 1988; Chao et al., 1999), and linked with severity of auditory hallucinations in schizophrenia (McGuire et al., 1995; Lennox et al., 2000). The current finding of temporal lobe overactivation that is uncorrelated with performance provides preliminary evidence that patients were less efficient in their auditory and linguistic processing of target words during episodic retrieval. Positive correlations between temporolimbic activation and severity of negative symptoms also suggest

that this excess activation was pathological rather than compensatory.

These temporal lobe areas provide primary inputs to the parahippocampal gyrus (Suzuki and Amaral, 1994; Tranel et al., 1988), which was also overactivated in patients during correct source retrieval. Abnormally increased parahippocamal activation may, therefore, reflect downstream effects of cortical overactivation. However, the parahippocampal gyrus has reciprocal connections with the hippocampus and plays an important role in episodic memory formation and retrieval. As noted by Henson and Rugg (2003), both human and animal studies demonstrate repetition-related decreases in parahippocampal activation, suggesting a role in familiarity based recognition. This familiarity based decrease does not appear dependent upon encoding context (Brown and Aggleton, 2001) and is, therefore, insufficient for source retrieval. Increased parahippocampal activation in patients could therefore represent an unanticipated failure in familiarity based retrieval. However, this account does not consider other network connections, and a more parsimonious explanation may be that overactivation is due to reduced functional connectivity in schizophrenia (Talamini et al., 2005).

Given previous findings of impaired source monitoring versus recognition performance in schizophrenia (Brébion et al., 1997; Keefe et al., 1999, 2002; Vinogradov et al., 1997) it is remarkable that patients were unimpaired in recognition and source retrieval. Unlike previous source monitoring experiments, the current study manipulated encoding strategy through the LOP paradigm. This paradigm appears effective in two respects; (a) during shallow encoding controls are inhibited from their natural tendency to engage in associative processing, and (b) during deep encoding patients are provided with the more effective strategy that is naturally adopted by controls. The only previous source monitoring study that provided semantic processing strategies had subjects generate semantic associates to target words and, nevertheless, found increased source attribution errors in patients (Moritz et al., 2003). We did find moderate to large effect sizes for performance accuracy and it is possible that the lack of group differences may have been partially due to reduced statistical power because of sample size. Nevertheless, our previous multinomial analysis of source monitoring (Ragland et al., 2006) also failed to find group differences in an expanded sample, with effect sizes remaining small. Thus, although it is possible that patients still have subtle impairments in source retrieval, it is clear that the magnitude of any such impairments is greatly reduced by providing patients with semantic encoding strategies.

There are several limitations. Because of our interest in differentiating correct word recognition with and without source recollection, true positive responses were divided into two classes (true positive, correct source and true positive, incorrect source). This reduced the number of events for modeling the HRF, particularly for controls in the true positive, incorrect source condition. This could be remedied in future studies by increasing the number of stimuli. However, we do not believe that this limitation could explain the finding of temporolimbic overactivation in patients because temporolimbic overactivation was also seen in the true positive, correct source condition in which there was a moderate effect for patients to have a lower number of responses. There were also several factors that may have reduced the generalizability of the data. All patients were medicated and clinically stable, with mild to moderate symptoms. This may have contributed to the lack of clinical correlations with positive symptoms, and reduces generalizability to more acutely ill and unmedicated samples. Source monitoring performance appears independent of medication status (Vinogradov et al., 1997) and there is little evidence of medication effects on prefrontal or mesial temporal activation during episodic memory (Heckers et al., 1998; Ragland et al., 2004; Weiss et al., 2003) (see Medoff et al., 2001 for exception). Nevertheless, it will be important to perform future studies in more acutely ill patients with prominent thought disorder and hallucinations to determine if temporolimbic overactivation is state related. The LOP paradigm is also not readily translatable to "real-world" situations in which patients must generate their own encoding strategies. However, the strength of recent behavioral and fMRI findings argues for increased investment in remediation. Even though training patients to engage in associative processing in new learning situations will not eliminate inefficiencies in their neural response, it will allow them to recruit necessary prefrontal brain regions and substantially remediate episodic retrieval deficits and likely improve daily function.

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