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Hippocampal dysfunction during declarative memory encoding in schizophrenia and effects of genetic liability

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ABSTRACT

Declarative memory (DM) impairments are reported in schizophrenia and in unaffected biological relatives of patients. However, the neural correlates of successful and unsuccessful encoding, mediated by the medial temporal lobe (MTL) memory system, and the influence of disease-related genetic liability remain under explored. This study employed an event-related functional MRI paradigm to compare activations for successfully and unsuccessfully encoded associative face-name stimuli between 26 schizophrenia patients (mean age: 33, 19 m/7f), 30 controls (mean age: 29, 24 m/6f), and 14 unaffected relatives of patients (mean age: 40, 5 m/9f). Compared to controls or unaffected relatives, patients showed hyper-activations in ventral visual stream and temporo-parietal cortical association areas when contrasting successfully encoded events to fixation. Follow-up hippocampal regions-of-interest analysis revealed schizophrenia-related hyper-activations in the right anterior hippocampus during successful encoding; contrasting successful versus unsuccessful events produced schizophrenia-related hypo-activations in the left anterior hippocampus. Similar hippocampal hypo-activations were observed in unaffected relatives during successful versus unsuccessful encoding. Post hoc analyses of hippocampal volume showed reductions in patients, but not in unaffected relatives compared to controls. Findings suggest that DM encoding deficits are attributable to both disease-specific and genetic liability factors that impact different components of the MTL memory system. Hyper-activations in temporo-occipital and parietal regions observed only in patients suggest the influence of disease-related factors. Regional hyper- and hypo-activations attributable to successful encoding occurring in both patients and unaffected relatives suggest the influence of schizophrenia-related genetic liability factors.

1. Introduction

Schizophrenia is characterized by a generalized cognitive impairment with pronounced deficits in memory and executive function (Reichenberg and Harvey, 2007; Ranganath et al., 2008). Specifically, patients with schizophrenia experience impairments in declarative memory (DM) (Aleman et al., 1999; Weiss and Heckers, 2001; Ranganath et al., 2008), which includes everyday memories of events (episodic memory) and facts (semantic memory) (Eichenbaum and Cohen, 2001). DM impairments are also reported in unaffected relatives of patients and increase with degree of biological relatedness, suggesting the involvement of schizophrenia genetic liability factors (Faraone et al., 2000; Whyte et al., 2005).

The hippocampus and medial temporal lobe (MTL) are essential for DM (Eichenbaum and Cohen, 2001). Prefrontal and posterior association regions also act to mediate memory processing (Sperling et al., 2010; Wang et al., 2010). Functional imaging studies of DM tasks in healthy subjects confirm MTL involvement and illustrate that regional activation is influenced by task characteristics, how information is learned, and whether encoding is successful (Buckner and Koutstaal, 1998; Preston et al., 2005).

DM relies on the successful encoding, storage, and retrieval of information. DM deficits in patients with schizophrenia and non-symptomatic relatives appear particularly attributable to encoding difficulties (Cirillo and Seidman, 2003). Since different network components contribute to the type and stage of DM processing (Brewer and Moghekar, 2002), encoding deficits may relate to dysfunctions confined

Abbreviations: (DM), declarative memory; (MTL), medial temporal lobe; (ROI), regions-of-interest; (AE), attempted encoding; (SE), successful encoding; (ESE), successful versus unsuccessful encoding.

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to specific MTL regions and/or to disturbances in connected cortical regions. Although more frequently focused on attempted encoding, several DM studies have demonstrated altered neural activity in hippocampal, parahippocampal, and connected prefrontal regions in schizophrenia (Heckers, 2001; Achim and Lepage, 2005; Ragland et al., 2009). Fewer fMRI studies have examined DM in unaffected relatives (MacDonald et al., 2009), and none have dissociated disturbances in regional activity by examining encoding success for associative stimuli exclusively.

To identify the subcomponents of the MTL memory system affected by schizophrenia and disease-related genetic liability, we employed a validated event-related fMRI design (Sperling et al., 2003) to compare blood-oxygen-level-dependent (BOLD) responses for successful DM encoding in schizophrenia patients, first-degree unaffected biological relatives of patients, and community controls. The DM task, including novel associative face-name stimuli, is shown to elicit MTL and regionally specific hippocampal activations during successful encoding in controls. We hypothesized that patients would show differences in the magnitude of task-related brain activity in the MTL and associated cortical regions. Further, we predicted that relatives of patients, sharing approximately half of their genes with schizophrenia probands, would show intermediate abnormalities. Since successful encoding elicits greater neural activity in the anterior hippocampus (Sperling et al., 2003), hippocampal regions-of-interest (ROI) analyses were also conducted. Finally, post hoc analysis of structural imaging data examined differences in hippocampal volumes across groups.

2. Methods

2.1. Subjects

Subjects included a sub-sample of participants enrolled in the University of California, Los Angeles (UCLA) Family Study (Nuechterlein et al., 2002; Yang et al., 2010, 2012). Community controls with demographics similar to schizophrenia probands were recruited using a survey research company. Seventy participants completed fMRI scanning with good quality data, including 26 patients, 14 unaffected first-degree relatives of patients and 30 controls (Table 1). Exclusion criteria included neurological disorders, mental retardation, and a history of drug or alcohol abuse.

Schizophrenia diagnosis was confirmed using the Structured Clinical Interview for DSM-IV–Patient version (SCID-I/P; (First et al., 2002)) and informant information. Symptoms were assessed using the expanded 24-item Brief Psychiatric Rating Scale (BPRS; (Ventura et al., 2000). All patients were receiving standard antipsychotic medication (risperidone: $n = 10$, olanzapine: $n = 4$, aripiprazole: $n = 5$, clozapine: $n = 2$, quetiapine: $n = 2$, fluphenazine: $n = 2$, not reported: $n = 2$). Controls and unaffected relatives of patients were screened to exclude schizophrenia spectrum disorders using the Structured Clinical Interview for DSM-IV–Nonpatient version (SCID-NP) and with the Structured Clinical Interview for DSM-IV Axis II Personality Disorders (SCID-II; (First et al., 1994)). The UCLA Institutional Review Board (IRB) approved all research procedures; informed written consent was obtained from all subjects.

2.2. Declarative memory task

The DM task, designed to dissociate changes in brain activity linked with attempted and successful encoding of face-name stimuli, included 455 color facial photographs varying in age, race, and gender selected from the National Institute of Standards and Technology, Facial Recognition Technology (FERET) database (Phillips et al., 1998). During scanning, each stimulus pair, a face with a unique and age-appropriate name, was presented once, intermixed with trials of visual fixation (0.25 to 10 s) using a jittered event-related design. Temporal parameters for this task were identical to those of Sperling et al., 2003. Subjects viewed stimuli through MR compatible goggles during 5 separate runs, each including 140 time points and 91 novel face-name stimuli. To facilitate encoding, subjects indicated whether the name "fit" the face simultaneously presented with a button press. Subjects were instructed to remember the face-name associations for a post-scan memory test.

2.3. Post-scan memory test

After scanning, a memory test that included the same face stimuli with a correct and incorrect name was administered. Subjects matched each face with its correct name and indicated whether they were

Table 1
Demographic and clinical characteristics of subjects.

	Schizophrenia patients ($N = 26$)		Patient relatives ($N = 14$)		Community controls ($N = 30$)	
	Mean	SD	Mean	SD	Mean	SD
Demographic measures						
Age (years)[a]	33.38	9.0	39.6	11.8	29.3	9.0
Current socioeconomic status[b]	35.5	15.1	47.9	21.3	44.8	18.4
Years of education[b]	14.1	1.9	14.9	2.4	15.3	2.6
Handedness (non-dextral/dextral)[b]	1/26		4/10		2/28	
Gender (male/female)[a]	19/7		5/9		24/6	
DM performance[a,c]						
Percent correct	68.1	6.1	69.0	6.8	70.6	7.1
Morphometric measures (cm^3)[b]						
Brain volume	1,421.81	141.62	1,324.44	151.57	1,427.77	141.55
Left hippocampal volume	4.41	.29	4.66	.22	4.58	.29
Right hippocampal volume	4.23	.31	4.43	.17	4.45	.28
Diagnostic measures						
Duration of illness (years)[b]	9.92	8.39				
BPRS total score[b]	38.13	9.25				
Withdrawal[c]	1.7	.70				
Thinking disorder[c]	1.6	.72				

[a] Patient relatives differed in age and gender with community controls and patients. Post-scan memory performance differed between patients and controls.
[b] Handedness was estimated from a modified version of the Edinburgh Handedness Inventory (Oldfield, 1971) where participants with a laterality quotient of >0.7 were defined as dextral. Handedness Information was missing for one patient and one control. Current social economic status was derived from the Total Socioeconomic Index (TSEI; Stevens and Cho, 1985). Data for socioeconomic status and years of education were unavailable for 5 subjects, duration of illness data for 1 subject, BPRS scores for 3 subjects, and volumetric data for 1 subject.
[c] BPRS scores were clustered into withdrawal (negative symptoms) and thinking disorder (positive symptoms) factor scores (Burger et al., 1997; Narr et al., 2009).

"guessing," "possibly correct," "probably correct," or "definitely correct." Correct "matches" and associated confidence ratings determined encoding success for events in subsequent fMRI analysis. However, since subjects applied this confidence scale subjectively, the 4 categories were re-binned into two categories, "high confidence" and "low confidence," based on responses definitely above chance. The three diagnostic risk groups did not differ with respect to the number of stimulus pairs rated with high or low confidence, $F(2, 61) = .45$, $p = .63$ or with respect to the number of stimulus pairs that were correctly rated with high, $F(2, 61) = .12$, $p = .86$ or low confidence $F(2, 61) = .41$, $p = .66$

2.4. Image acquisition

Functional T_2*-weighted gradient echo and echo-planar images were acquired on a Siemens 3T Allegra system (Milwaukee, WI) at the UCLA Ahmanson-Lovelace Brain Mapping Center. To maximize in-plane resolution (3.1 mm × 3.1 mm) and to minimize susceptibility artifacts within the hippocampus, acquisition included 26 slices (5 mm, interslice distance, 1 mm), positioned in the oblique coronal orientation (TR/TE: 2000/30 ms, flip angle: 90, matrix: 64 × 64; FOV: 200; total scan time: 23.5 min). A non-BOLD T2-weighted image acquired co-planar to the time series data (TR/TE: 5000/33 ms, flip angle: 90, matrix: 128 × 128; FOV: 200; scan time: 1.5 min) was collected on the same system. In addition, high-resolution T1-weighted MPRAGE scans (TR/TE: 1900/4.38 ms, TI = 1100; flip angle: 15; FOV: 256; matrix: 256 × 256; voxel size: 1 mm^3; averages = 4; total scan time = 32.32 min) were acquired on a Siemens 1.5 T Sonata scanner to facilitate multimodal within- and across-subject registration and estimate hippocampal volumes.

2.5. Data analysis

FMRI analysis followed the scheme outlined by Sperling et al. using FSL's (www.fmrib.ox.ac.uk/fsl) fMRI Expert Analysis Tool (FEAT), version 5.98. Preprocessing included removal of non-brain tissue, motion correction, spatial smoothing (6 mm FWHM), denoising, and high-pass filtering (70 s cutoff). All data were inspected, and residual motion was controlled for using six rigid body movement parameters as regressors when modeling the BOLD response. FLIRT registered fMRI data across runs and with the T2 and T1-weighted images. For higher-level analyses, the T1-weighted images were registered to the MNI 152 average image (Grabner et al., 2006).

FSL's FILM (FMRIB's Improved Linear Model) compared the following: (1) all stimulus trials versus fixation to model attempted encoding (AE), (2) high-confidence correct trials versus fixation to model successful encoding (SE), and (3) high-confidence correct versus incorrect trials to model activations exclusive to successful encoding (ESE), i.e., separate from processes associated with the memory task in general. Group by contrast interactions were assessed for contrasts 2 and 3 above to establish differences in brain activation for SE and ESE (Fig. 1).

Mixed effects modeling, using FSL's FLAME (FMRIB's Local Analysis of Mixed Effects), determined significant differences in regional activation between groups controlling for age, gender, and post-scan memory performance using cluster correction and a z-threshold = 1.7, $p < .05$. For significance testing, cluster size inference based on Gaussian random field theory (Hayasaka and Nichols, 2003) compared (1) patients to controls, (2) relatives to controls, and (3) patients to relatives.

Since AE, SE, and ESE may lead to differential engagement of the hippocampus, anatomical ROIs were also used to examine focal hippocampal activations across groups. Hippocampal labels generated from the Harvard-Oxford probabilistic atlas were linearly registered to each subject's functional data in each hemisphere and subsequently separated into anterior and posterior halves (bisecting midway across the longest oblique axis of the hippocampus) (Greicius et al., 2003) to visualize percent signal change within each segment.

Hippocampal volumes (including the subiculum) were estimated from each subject's T1-weighted image using FreeSurfer's image analysis suite (http://surfer.nmr.mgh.harvard.edu/). In brief, preprocessing of T1 data included the removal of non-brain tissue, intensity normalization, and automated volumetric segmentation of the hippocampus using established and well-validated and documented procedures that make use of probabilistic information based on manually labeled training sets (Fischl et al., 2002, 2004; Fischl, 2012). Each hippocampal segmentation was visually inspected, and any small segmentation errors were corrected manually. A repeated-measures ANCOVA was used to test for group differences in hippocampal volume.

3. Results

3.1. Demographic variables and performance

Table 1 includes demographic, clinical, and memory performance information by group. Patients and controls were similar in age, $F(1, 54) = 2.86$, $p = .10$, and gender, $\chi^2(1, 49) = .01$, $p = .94$; all groups were of similar socioeconomic status, $F(2, 61) = 2.59$, $p = .08$. However, relatives were older than controls ($F(1, 42) = 10.33$, $p < .01$, although not older than patients, $p > .07$. Relatives also differed in gender compared to patients and controls ($\chi^2(1, 43) = 8.33$, $p < .01$ and $\chi^2(1, 39) = 6.54$, $p = .01$). Although performing above chance, patients showed poorer memory performance than controls, $F(1, 48) = 7.94$,

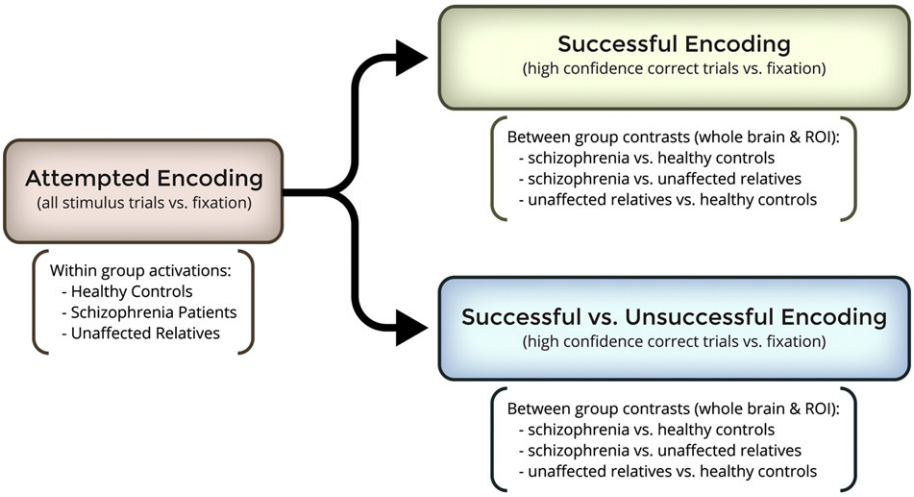

Fig. 1. Diagram of the experimental design and fMRI contrasts included for study.

$p < .01$. Relatives did not differ in performance from patients $p > .7$ or controls $p > .09$ (Table 1). Age, gender, and performance from the post-scan memory test were included as covariates in all fMRI analysis.

3.2. Attempted encoding

In line with previous findings (Sperling et al., 2003; Zeineh et al., 2003), AE was associated with activation in bilateral hippocampal, fusiform, ventral visual stream regions, thalamic, striatal, and lateral and ventral prefrontal regions within each group (Fig. 2, Table 2).

3.3. Successful encoding

We examined SE by comparing activation during high-confidence correct trials versus fixation. Patients showed significant hyper-activations in bilateral ventral visual stream (fusiform and lingual gyri and medial and lateral occipital cortex), temporo-parietal association (precuneus and lateral superior and inferior parietal lobules), and sensorimotor areas compared to controls (Fig. 3a, Table 3). Although not identified as a peak activation, activity in the right anterior hippocampus was also greater in patients (Fig. 3a). Schizophrenia-related hyper-activations were observed in similar regions when patients were compared to relatives (Fig. 3b, Table 3). Relatives showed decreased activation in the superior temporal gyrus and fusiform areas compared to controls (Fig. 3c, Table 3).

ROI analyses of SE revealed significant hyper-activation in the right anterior hippocampus in patients compared to controls (Fig. 4a) and in the right posterior hippocampus when compared to relatives (Fig. 4b). Relatives showed decreased activation in the right posterior hippocampus compared to controls (Fig. 4c).

3.4. Exclusive successful encoding

Whole brain analysis revealed no significant differences in brain activation between the three diagnostic risk groups for ESE. However, within ROIs, patients showed significant hypo-activation of the left anterior hippocampus compared to controls (Fig. 5a), but no difference from relatives (Fig. 5b). Similar to patients, relatives showed hypo-activation in the left anterior hippocampus compared to controls (Fig. 5c).

3.5. Hippocampal volume

Significant reductions in hippocampal volume were observed in patients compared to controls, $F(1,49) = 5.01$, $p = .03$, and relatives, $F(1,33) = 4.35$, $p = .045$, but not between relatives and controls, $p > .59$, covarying for age, gender, and brain volume (Table 1, Fig. 6). Although mean volumes were larger in the left versus the right hemisphere, there were no significant effects of asymmetry ($p > .05$)

4. Discussion

Several novel findings emerged from whole brain and hippocampal ROI analysis of SE and ESE in schizophrenia patients, unaffected relatives and controls. While all groups showed similar activation in MTL and connected prefrontal and subcortical centers, SE was associated with increased activity in temporo-occipital (ventral visual stream) and parietal association areas in patients compared to the non-schizophrenia groups. In ROI analysis, the observed increased activity in the right anterior hippocampus of patients suggests the influence of disease-related effects. In contrast, during ESE, decreased activity observed in the left

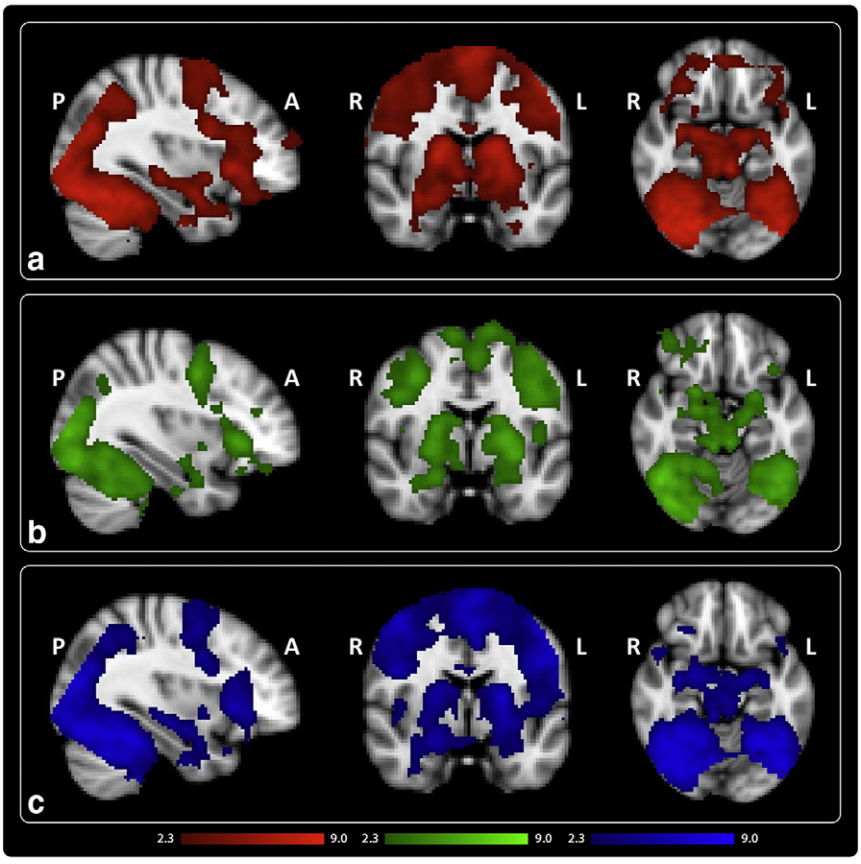

Fig. 2. Mean activation for attempted encoding of associative face-name stimuli shown in (a) controls (red), (b) unaffected relatives of patients (green), and (c) patients (blue) ($z > 2.3$, $p < .05$, corrected).

Table 2
Attempted encoding (within group peak activations).

Contrast	Group	Cortical Region[a]	x	y	z	Z-score
Attempted Encoding (fixation vs. task)	Controls	29% lingual gyrus, 28% occipital fusiform gyrus	14	−82	−12	9.10
		75% lingual gyrus, 13% intracalcarine cortex	0	−76	0	9.09
		67% occipital fusiform gyrus, 9% lingual gyrus	24	−76	−14	8.77
		66% temporal occipital fusiform cortex, 7% temporal fusiform cortex, 5% inferior temporal gyrus	−36	−50	−22	8.57
		29% occipital fusiform gyrus, 6% lateral occipital cortex, 5% inferior temporal gyrus	40	−66	−20	8.46
		70% temporal occipital fusiform cortex	38	−50	−22	8.45
		35% right thalamus, 17% right hippocampus	22	−30	−4	8.96
		79% brain stem	8	−32	−4	8.25
		9% left thalamus	−22	−28	−4	7.96
		30% inferior frontal gyrus, 18% middle frontal gyrus	−40	18	24	7.09
		63% paracingulate gyrus	2	12	48	7.43
		41% precentral gyrus, 23% inferior frontal gyrus	46	8	26	7.41
	Unaffected relatives	36% inferior temporal gyrus 26% lateral occipital cortex, 17% temporal occipital fusiform cortex	48	−60	−16	7.07
		49% lateral occipital cortex	30	−76	20	6.84
		40% lateral occipital cortex, 22% occipital fusiform gyrus	38	−80	−14	6.78
		35% lateral occipital cortex, 15% occipital pole, 15% lateral occipital cortex	36	−86	4	6.59
		74% temporal occipital fusiform cortex, 7% inferior temporal gyrus	40	−48	−22	6.56
		30% lingual gyrus, 25% occipital fusiform gyrus, 8% occipital pole	14	−86	−10	6.39
		69% lateral occipital cortex	−46	−82	−4	7.26
		35% lateral occipital cortex, 16% lateral occipital cortex, 13% occipital pole	−36	−88	12	6.99
		38% inferior temporal gyrus, 20% lateral occipital cortex, 14% occipital fusiform gyrus, 5% temporal occipital fusiform cortex	−44	−62	−10	6.87
		56% temporal occipital fusiform cortex, 16% inferior temporal gyrus, 5% occipital fusiform gyrus	−42	−56	−22	6.44
		57% lateral occipital cortex, 6% lateral occipital cortex	−42	−84	4	6.23
	Patients	70% Temporal occipital fusiform cortex, 6% inferior temporal gyrus, 5% occipital fusiform gyrus	−38	−56	−20	8.27
		57% lateral occipital cortex, 12% occipital fusiform gyrus	−46	−70	−12	8.24
		41% lingual gyrus, 19% occipital fusiform gyrus, 4% occipital pole	12	−84	−10	8.24
		68% lateral occipital cortex	−44	−80	−6	8.08
		48% occipital fusiform gyrus, 11% lateral occipital cortex, 6% temporal occipital fusiform cortex, 5% inferior temporal gyrus	40	−66	−18	8.06
		54% lateral occipital cortex	30	−78	20	8.03
		42% right thalamus, 36% right hippocampus	20	−32	−4	8.34
		42% precentral gyrus, 19% inferior frontal gyrus, 7% middle frontal gyrus	−52	8	30	7.48
		100% left thalamus	−8	−20	6	7.15
		72% juxtapositional lobule cortex	−2	2	54	7.20
		48% precentral gyrus, 8% inferior frontal gyrus	48	6	28	7.69

[a] Cortical regions with probabilities < 5% were excluded.

anterior hippocampus in both patients and relatives compared to controls suggests schizophrenia genetic liability effects.

Together these findings suggest that disease-related and genetically mediated alterations in circuitry both intrinsic and extrinsic to the MTL memory system contribute towards altered DM processing in schizophrenia. Differential hippocampal activity points to interacting processes. For example, increased hemodynamic response for SE observed in patients may indicate over-recruitment, lack of inhibition, more effortful and/or prolonged processing during SE (Kuperberg et al., 2007). Conversely, reduced activation of the left anterior hippocampus for ESE, suggest simultaneous under-recruitment of sub-regions that reflect a failure to organize information at the early stages of learning and lead to over compensation and hyper-activations in other components of the MTL circuit.

4.1. Medial temporal lobe

Several reviews indicate that DM impairments are pronounced in schizophrenia (Heinrichs and Zakzanis, 1998; Aleman et al., 1999) and occur in relatives of patients (Faraone et al., 2000; Toulopoulou et al., 2003). These observations together with postmortem and structural neuroimaging evidence suggest hippocampal and MTL function are central in the pathophysiology of schizophrenia (Heckers, 2001; Harrison, 2004). Still, few studies have focused on the neural processes underlying successful associative encoding (Ranganath et al., 2008). Partially in line with our findings, meta-analytic results show *increased* activation in parahippocampal regions during the encoding of episodic memories in schizophrenia (Ragland et al., 2009). The use of item-based rather than associative stimuli, which generally produce more robust hippocampal activation (Davachi and Wagner, 2002; Henson and Gagnepain, 2010), may account for sub-threshold hippocampal activity in patients and controls in prior studies.

In concordance with our results, an fMRI investigation of different encoding tasks demonstrated that schizophrenia patients activate hippocampal and overlying MTL regions during associative and successful memory encoding (Achim et al., 2007). However, patients also showed decreased activation within hippocampal and surrounding temporolimbic regions during the encoding of arbitrary stimulus pairs. These findings indicate that although patients are able to recruit MTL regions, altered function in particular aspects of this system, including differential contributions of the hippocampus, occur during encoding. Evidence suggests the successful encoding of face-name pairs induces greater activity in anterior hippocampal regions (Sperling et al., 2003). By employing small volume correction, considered a more powerful approach for determining focal changes in hippocampal activation (MacDonald et al., 2009), the present investigation showed schizophrenia-related hyper- and hypo-activations in the right and left anterior hippocampus for SE and ESE respectively. This suggests deficits and compensatory mechanisms in DM circuits, potentially lateralized for verbal and non-verbal processing of face-name pairs.

Hippocampal abnormalities and disturbances in episodic memory have been recognized as possible endophenotypes of schizophrenia genetic liability (Narr et al., 2002; Toulopoulou et al., 2003; Snitz et al., 2006; Boos et al., 2007). Although no published studies have examined

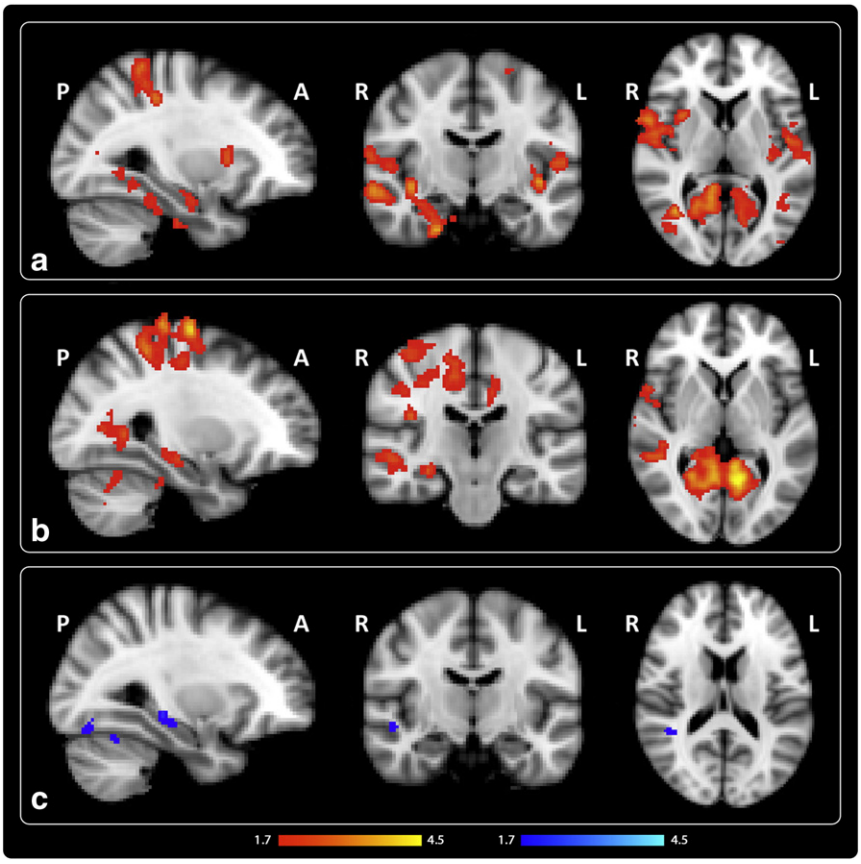

Fig. 3. Successful encoding in patients is associated with increased activations in multiple brain areas. Regions showing increased activation in red and decreased activation in blue for high-confidence correct trials versus fixation in (a) patients compared to controls, (b) patients compared to unaffected relatives, and (c) unaffected relatives compared to controls ($z > 1.7$, $p < .05$, corrected).

associative encoding for successfully recalled events in unaffected relatives, an investigation of novel and repeated word-pair encoding—although addressing attempted encoding only—showed greater repetition suppression in bilateral anterior parahippocampal regions in relatives of patients (Thermenos et al., 2007) as partially consistent with our results.

In line with prior studies (Nelson et al., 1998; Wright et al., 2000; Honea et al., 2005), schizophrenia patients showed significantly smaller hippocampal volumes (Table 1, Fig. 6). Several studies support relationships between hippocampal structure and DM performance (Antonova et al., 2004; Thoma et al., 2009; Herold et al., 2013), suggesting altered activation may relate to abnormal macrostructure. The absence of

Table 3
Successful encoding (peak activations).

Contrast		Cortical region[a]	Hemisphere	*x*	*y*	*z*	*Z*-score
Successful Encoding (high-confidence correct vs. fixation)	Patients vs. controls	31% cuneal cortex, 27% precuneus cortex, 8% supracalcarine cortex, 6% intracalcarine cortex	Left	−12	−72	22	4.35
		40% insular cortex, 25% planum polare	Left	−42	−10	−6	4.20
		35% superior parietal lobule, 21% postcentral gyrus, 6% supramarginal gyrus	Left	−32	−40	58	3.94
		35% cuneal cortex, 29% precuneus cortex, 13% supracalcarine cortex	Right	12	−68	24	4.12
		32% precentral gyrus, 5% inferior frontal gyrus	Right	64	8	10	4.04
		20% lateral occipital cortex	Right	38	−62	8	3.87
	Patients vs. unaffected relatives	61% lingual gyrus, 13% precuneus cortex	Left	−10	−58	2	4.60
		44% superior parietal lobule, 18% postcentral gyrus, 5% supramarginal gyrus	Left	−30	−42	64	3.92
		42% postcentral gyrus, 7% precentral gyrus	Left	−24	−34	58	3.62
		38% intracalcarine cortex	Right	22	−68	8	4.29
		43% precentral gyrus, 6% superior frontal gyrus	Right	28	−12	70	4.03
		52% precentral gyrus, 11% middle frontal gyrus	Right	44	−4	60	4.01
		40% middle temporal gyrus, 36% superior temporal gyrus	Right	60	−16	−8	3.39
	unaffected relatives vs. controls	46% superior temporal gyrus, 15% middle temporal gyrus, 5% supramarginal gyrus	Right	46	−30	0	3.29
		28% middle temporal gyrus, 10% supramarginal gyrus, 6% middle temporal gyrus	Right	46	−40	4	3.11
		23% lingual gyrus, 17% occipital fusiform gyrus	Right	12	−74	−14	3.16

[a] Cortical regions with probabilities <5% were excluded.

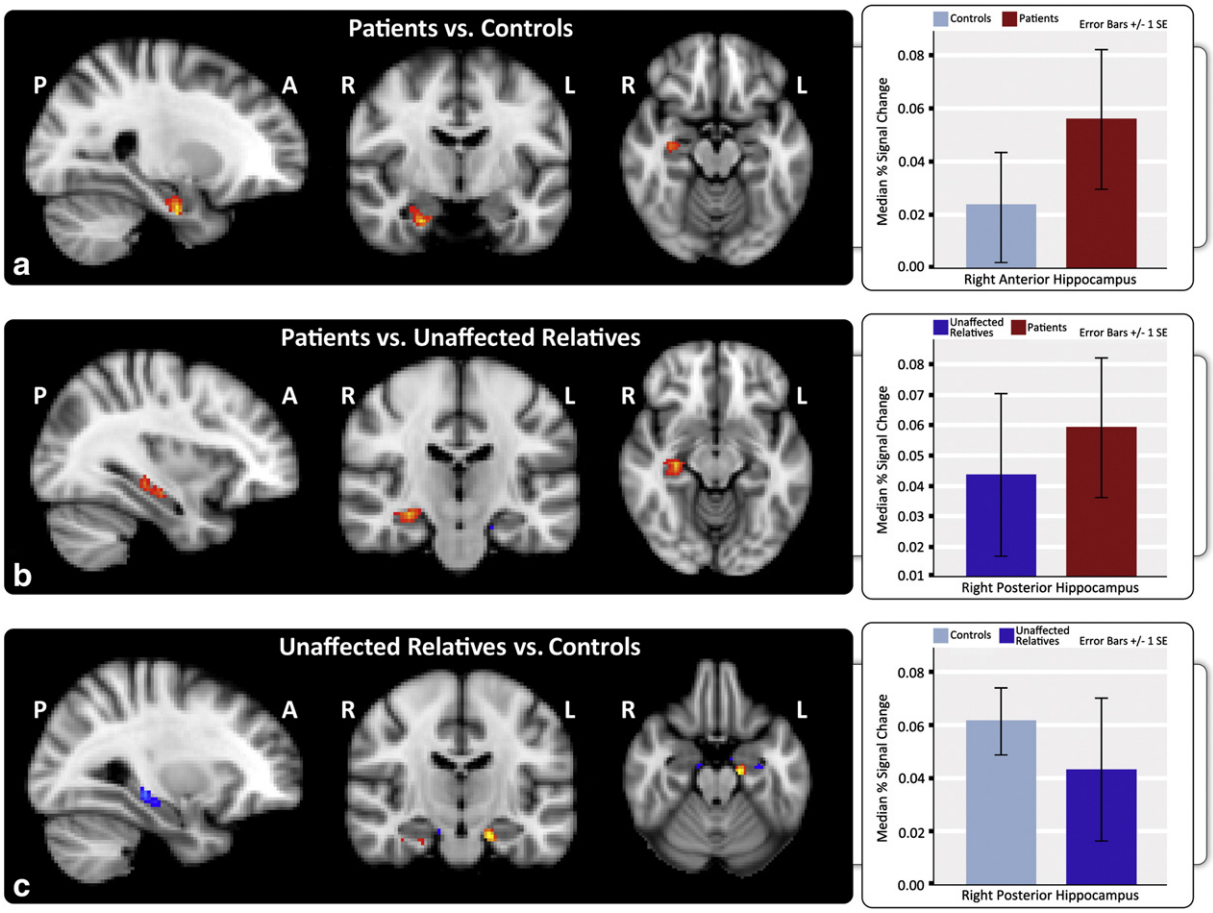

Fig. 4. Hippocampal ROI analysis shows successful encoding is associated with increased hippocampal activation in schizophrenia patients compared to controls and unaffected relatives. Increased activation is shown in red and decreased activation in blue for high-confidence correct trials versus fixation in (a) patients compared to controls, (b) patients compared to unaffected relatives, and (c) unaffected relatives compared to controls. Graphs show the estimated median percent signal change within anatomically defined anterior and posterior hippocampal regions in each hemisphere for each diagnostic group.

reduced hippocampal volumes in relatives implies that abnormalities in hippocampal function can occur without observed differences in structure.

4.2. Cortical association regions

Prior schizophrenia studies have shown altered DM-related activation of prefrontal regions; meta-analytic results suggest largest effects in ventro- and dorso-lateral prefrontal cortex (Ragland et al., 2009). In this study, all groups showed activation in inferior prefrontal cortex during AE (Fig. 2), although group effects were mostly absent (Table 3). Since prefrontal recruitment may relate to higher-level processes, including cognitive strategies used to facilitate encoding (Reber et al., 2002; Blumenfeld and Ranganath, 2007), the absence of robust differences in prefrontal regions may be a consequence of our study design, which did not manipulate encoding strategies or difficulty.

Patients showed increased activity in several other neocortical association areas compared to non-schizophrenia groups during SE. Specifically, hyper-activations in ventral visual stream, fusiform/lingual, and fusiform/parahippocampal regions, areas involved in the perception of faces and objects (Grill-Spector et al., 2004; Kanwisher and Yovel, 2006), may reflect impairments in tasks involving face discrimination (Whittaker et al., 2001; Pinkham et al., 2005). Other fMRI studies have shown fusiform dysfunction in schizophrenia during face processing (Quintana et al., 2003; Walther et al., 2009; Silverstein et al., 2010) that may represent deficits specific to configural processing at early stages of discrimination (Shin et al., 2008) and/or impairments of integration (Silverstein et al., 2010). Although prior studies also suggest impairments in face discrimination in unaffected relatives (Calkins et al., 2005), these effects were not observed in the current study.

Increased activation was also observed in parietal association areas including the precuneus and in superior temporal regions in patients compared to non-schizophrenia groups. These cortical association areas are reciprocally connected with the parahippocampus, with primary input to the hippocampus. These regions are involved in integrated perceptual processing (Eichenbaum and Cohen, 2001) and may contribute to conscious and effortful organization of information during encoding (Bearden et al., 2012). Reports of increased activation in parietal and superior temporal/insular regions have been observed in at least one prior study during SE in schizophrenia (Achim et al., 2007), suggesting DM processing relies on networks extrinsic to, but intricately connected with the MTL.

4.3. Limitations

Although negative symptoms may impact DM, prior evidence suggests that DM deficits in schizophrenia are independent of age, duration of illness and positive symptoms (Goldberg and Weinberger, 1996; Aleman et al., 1999; Bilder et al., 2000; Cirillo and Seidman, 2003). Since patients were relatively asymptomatic at assessment (Table 1), we could not address these relationships. Prior evidence also suggests that antipsychotic medications have little impact on memory performance (Goldberg and Weinberger, 1996; Gilbertson and van Kammen, 1997; Aleman et al., 1999; McGurk, 1999). Although influences of performance on the hemodynamic response are less clear, relatives who were not receiving medication also showed altered brain activity

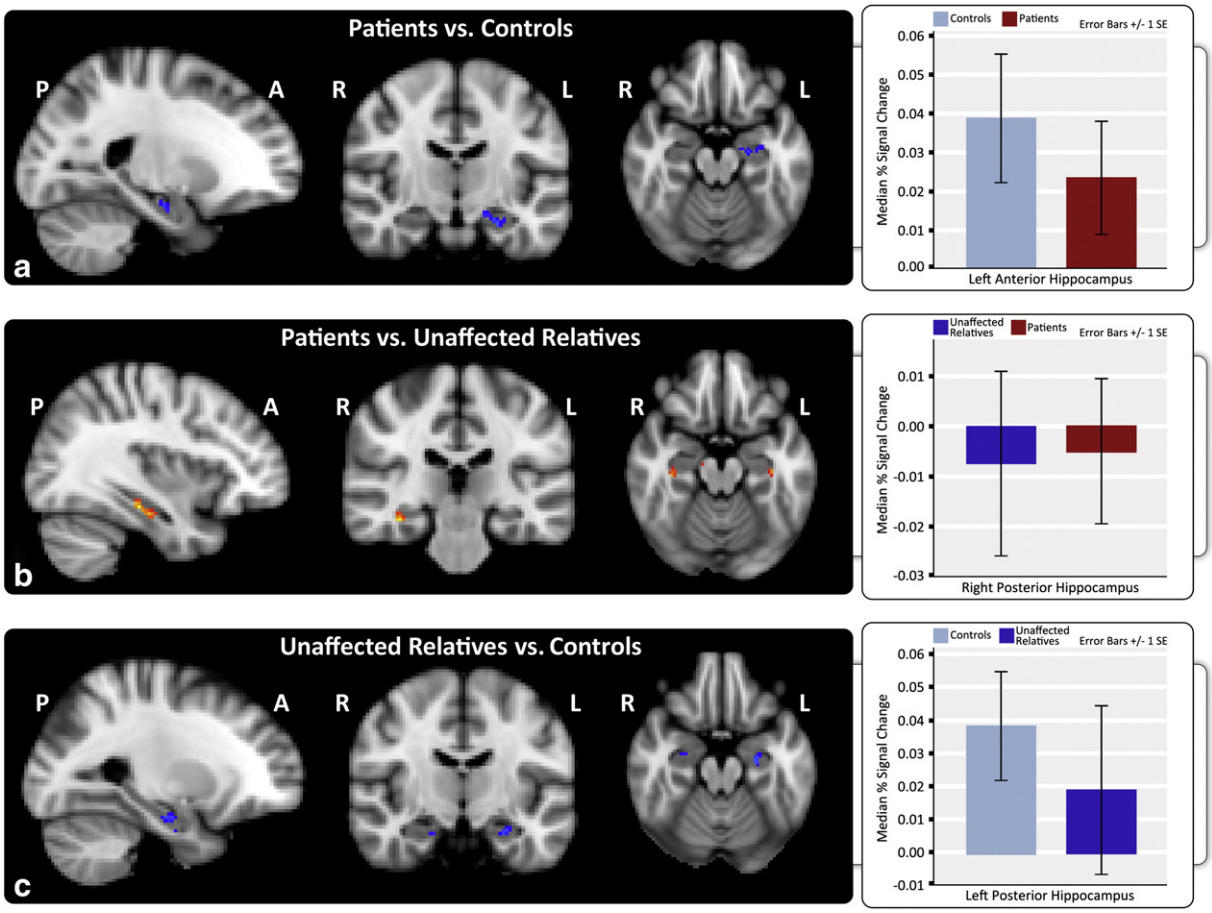

Fig. 5. Retrieval success in exclusive successful encoding is associated with reductions in hippocampal activation in schizophrenia patients. Hippocampal ROIs showing increased activation in red and decreased activation in blue for high-confidence correct versus incorrect trials in (a) patients compared to controls, (b) patients compared to unaffected relatives, and (c) unaffected relatives compared to controls. Graphs show the estimated median percent signal change within anatomically defined anterior and posterior hippocampal regions in each hemisphere for each diagnostic group.

under particular task conditions. Finally, although gender and age were controlled for in all analyses, differences in age and smaller sample size of the relative group may have impacted our ability detect additional genetic liability effects with respect to regional brain activations or changes in hippocampal volume.

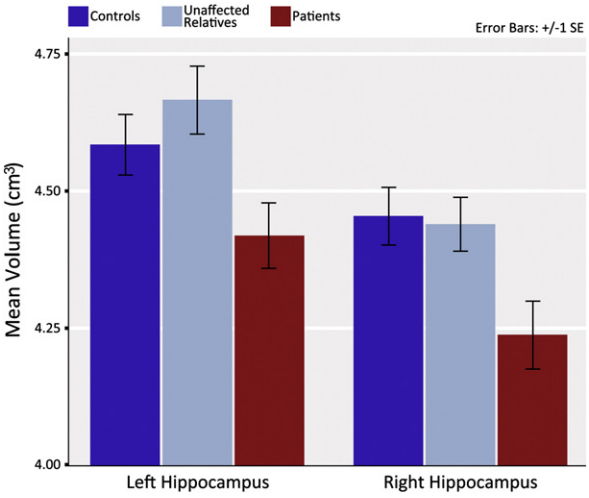

Fig. 6. Schizophrenia patients exhibit significant decreases in left and right hippocampal volume compared to controls and unaffected relatives. Graph shows mean left and right hippocampal volumes for controls, unaffected relatives, and patients after correcting for sex and age and brain volume.

4.4. Conclusion

Altered brain activity during DM encoding in schizophrenia points to the involvement of both disease-specific and schizophrenia-related genetic liability factors. Results support that (1) DM encoding deficits impact different components of the MTL memory system and connected association regions, and (2) altered activity in the anterior hippocampi vary according to encoding success and genetic predisposition. DM has been shown as predictor of poor social and occupational functioning in schizophrenia (Bilder et al., 2000; Green et al., 2000). Thus, a better understanding of the underlying mechanisms may help direct efforts to improve social-vocational outcome. Due to the heritability of DM (Manns and Eichenbaum, 2006), findings in unaffected relatives suggest further clues regarding the genetic basis of schizophrenia.

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Author contributions

All authors made substantive contributions the work presented in this paper. K.L.N. designed and implemented the study. R.P.W. supervised experimental design and methods. T.P. performed data analysis and drafted the manuscript. L.S.H. helped develop analytic tools and with K.L.N. conducted data acquisition. S.J. and H.L. contributed to data analysis. All authors, including R.F.A and K.H.N., participated in data interpretation and commented on the manuscript.

Conflict of interest

The authors have no conflicts to disclose.

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