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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).