



Impact of schizophrenia on anterior and posterior hippocampus during memory for complex scenes



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ABSTRACT

Objectives: Hippocampal dysfunction has been proposed as a mechanism for memory deficits in schizophrenia. Available evidence suggests that the anterior and posterior hippocampus could be differentially affected. Accordingly, we used fMRI to test the hypothesis that activity in posterior hippocampus is disproportionately reduced in schizophrenia, particularly during spatial memory retrieval.

Methods: 26 healthy participants and 24 patients with schizophrenia from the UC Davis Early Psychosis Program were studied while fMRI was acquired on a 3 Tesla Siemens scanner. During encoding, participants were oriented to critical items through questions about item features (e.g., “Does the lamp have a square shade?”) or spatial location (e.g., “Is the lamp on the table next to the couch?”). At test, participants determined whether scenes were changed or unchanged. fMRI analyses contrasted activation in a priori regions of interest (ROI) in anterior and posterior hippocampus during correct recognition of item changes and spatial changes.

Results: As predicted, patients with schizophrenia exhibited reduced activation in the posterior hippocampus during detection of spatial changes but not during detection of item changes. Unexpectedly, patients exhibited increased activation of anterior hippocampus during detection of item changes. Whole brain analyses revealed reduced fronto-parietal and striatal activation in patients for spatial but not for item change trials.

Conclusions: Results suggest a gradient of hippocampal dysfunction in which posterior hippocampus – which is necessary for processing fine-grained spatial relationships – is underactive, and anterior hippocampus – which may process context more globally – is overactive.

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1. Introduction

Episodic memory impairment is a core symptom of psychotic disorders such as schizophrenia (Achim and Lepage, 2003, 2005; Titone et al., 2004; Ranganath et al., 2008; Ragland et al., 2015), and this deficit is likely related to impaired hippocampal function. Basic behavioral and cognitive neuroscience research reveals important functional differences across the longitudinal extent of the anterior and posterior hippocampus. However, it is unclear whether the anterior and posterior hippocampus is differentially affected in schizophrenia.

Research in rodents demonstrates that the dorsal (corresponding to posterior in humans) and ventral hippocampus (corresponding to anterior in humans) differ in terms of anatomical connectivity and gene

expression (Fanselow and Dong, 2010; Strange et al., 2014). Furthermore, lesions to the dorsal hippocampus in rats impair performance on spatial memory tasks, whereas ventral hippocampal lesions often have no effect on spatial learning (Moser and Moser, 1998; Bannerman et al., 2004). Studies of place cells in rats complement lesion findings by suggesting that place cells in dorsal hippocampus exhibit specific place fields, whereas place cells in ventral hippocampus are often large, sometimes extending across an entire spatial context (Kjelstrup et al., 2008; Keinath et al., 2014).

Dissociations between anterior and posterior hippocampal functions have also been observed in humans with fMRI (Strange et al., 2014). Functional dissociations between anterior and posterior hippocampus have been attributed to processing of; novel versus repeated stimuli (Ranganath and Rainer, 2003; Strange et al., 2005; Kumaran and Maguire, 2006), emotional versus non-emotional material (Gray and McNaughton, 1982; Murty et al., 2010) and encoding versus retrieval (Spaniol et al., 2009). Work has also linked posterior hippocampus to retrieving memories based on spatial context information, and anterior hippocampus to more global and less context-dependent relational memory processes (Hannula et al., 2013). Moreover, when processing

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spatial information, a distinction exists between retrieval of fine-grained spatial details (posterior hippocampus) versus more global gist-like information (anterior hippocampus). This has contributed to a “granularity gradient” model in which the head of the hippocampus retrieves coarse, large-scale representations; the hippocampal body retrieves medium sized spatial representations; and the tail of the hippocampus retrieves fine-grained local representations (Poppenk et al., 2013; Evensmoen et al., 2015). Based on this granularity model, we predict that manipulation of spatial locations during the current memory task will produce maximal activation in the posterior hippocampus, whereas the anterior hippocampus will be most sensitive to global changes in item identity.

This distinction between anterior and posterior hippocampal function has received minimal attention in the schizophrenia literature. The most consistent story comes from resting-state studies supporting a model of tonic hyperactivity of the anterior hippocampus in patients versus healthy controls (Grace, 2012). According to this view, increased activity of the ventral/anterior hippocampus leads to disinhibition of the ventral tegmental area, and this, in turn, contributes to increased dopaminergic activity and disordered cognition in schizophrenia (Lodge and Grace, 2011; Grace, 2012). Consistent with this idea, a series of resting-state studies of cerebral blood volume (CBV) (Schobel et al., 2009; Schobel et al., 2013; Talati et al., 2014), found that CBV was increased in patients relative to healthy controls specifically within the CA1 region of the anterior hippocampus [for review, see (Heckers and Konradi, 2015)]. It is unclear how this tonic hyperactivity would relate to specific episodic memory functions, although an early study suggested that a hyperactive baseline state could help explain the reduced responsivity of the hippocampus to memory demands (Weiss et al., 2003).

With one exception (Tamminga et al., 2012), fMRI studies of episodic memory in schizophrenia have not systematically examined anterior versus posterior hippocampus. In an attempt to detect a consistent anterior/posterior pattern of group differences we performed a qualitative review and found roughly an equal number of studies that; 1) employed tasks that failed to engage the hippocampus or detect group differences in either anterior or posterior hippocampus (Ragland et al., 2004; Bonner-Jackson et al., 2005; Ragland et al., 2005; Lepage et al., 2006), 2) utilized designs that were successful in detecting reduced activation in patients, relative to healthy controls, in the anterior hippocampus (Ongur et al., 2006; Tamminga et al., 2012; Ragland et al., 2015), or 3) utilized tasks that revealed evidence of reduced patient activation in the posterior hippocampus during episodic retrieval (Heckers et al., 1998; Weiss et al., 2003; Achim and Lepage, 2005). The one study that directly contrasted anterior and posterior hippocampus found that anterior hippocampal activity increased during novelty detection in healthy controls, and was reduced in unmedicated but not in medicated people with schizophrenia (Tamminga et al., 2012).

Based on findings indicating potentially different effects on anterior and posterior hippocampus, the goal of the current study was to test the hypothesis that patients with schizophrenia are specifically impaired at activating the posterior hippocampus during episodic retrieval. Participants were scanned while performing a memory paradigm that required detection of subtle changes to items or spatial configurations in complex visual scenes (Hannula et al., 2010a). In a previous eye-tracking study using a variant of the current task (Hannula et al., 2010a), we found that patients with schizophrenia spent less time viewing the portion of a scene that involved a spatial change in item location, but showed a normal increase in viewing when there was change in item identity, suggesting a disproportionate eye-movement memory deficit for spatial information. Based on findings indicating posterior hippocampal specialization for fine-grained spatial relationships and spatial context (Hannula and Ranganath, 2008; Poppenk et al., 2013; Evensmoen et al., 2015), we hypothesized that patients with schizophrenia would show relative reductions in posterior, but not anterior hippocampal activation during processing of spatial changes.

2. Methods and materials

2.1. Participants

Data were acquired on 30 patients with schizophrenia and 30 healthy controls. Data were excluded for excessive relative frame-to-frame movement (i.e., >0.4 mm, exceeding 3 standard deviations from the mean) in 1 control and 1 patient; for below chance performance in 1 control and 2 patients; for 1 control and 2 patients who stopped participation; for 1 control with an incidental abnormal anatomical finding; and for 1 patient with a technical malfunction (faulty button box), leaving a final sample of 24 patients with schizophrenia and 26 controls. Groups were matched for age, gender, handedness and parental education (Table 1). Participant education was lower in patients. All patients were receiving medication (2 typical, 22 atypical), and clinically stable. Patients were early in their illness [Duration (mean \pm standard deviation) = 3.02 \pm 2.51 years], and overall symptom severity (BPRS total) was in the mild range (42.7 \pm 13.3). Data collection began after participants provided written informed consent following Institutional Review Board approval.

2.2. Materials

Stimuli included 128 rendered scenes created using Punch! Home Design software (Encore, Inc., El Segundo, CA). Three scene variants were created – the original, a version containing an item manipulation, and a version containing a spatial manipulation – producing a total of 384 scenes. One item embedded in each original scene was designated the *critical item* and, in manipulated versions, this item was either replaced with a different exemplar (item change) or displaced and moved to a new location (spatial change). Critical items were presented in the context of just one scene, and moved equally often from left (in the original scene) to right (in the changed scene) as right to left when the change was spatial.

During encoding (Fig. 1a), participants were presented with orienting questions, directing their attention to the critical item, and were asked either about item features (e.g., “Does the lamp have a square shade?”) or spatial location (e.g., “Is the lamp on the table next to the couch?”). These questions ensured that participants attended to and encoded critical items that might subsequently change during the test phase (Hannula et al., 2010a; Hannula, Tranel & Cohen, 2006). The experiment was designed so that the type of change at test (item or spatial) was always consistent with processing required by the initial orienting question.

2.3. Methods

After informed consent, each participant successfully completed a practice session before being situated in the fMRI scanner with head

Table 1
Demographic characteristics of research participants.

	Healthy control group (n = 26)		Patients with schizophrenia (n = 24)		p-Value
	Mean	SD	Mean	SD	
Age (years)	23.1	3.5	25.2	4.2	ns
Gender (% male)	4 F, 22 M		6 F, 18 M		ns
Handedness	1 left		2 left		ns
Education (years)	14.8	1.4	13.1	1.9	<0.1
Parental education (years)	15.6	2.9	14.8	3.4	ns
BPRS (total)			42.7	13.3	

Note: SANS = Scale for the Assessment of Negative Symptoms; SAPS = Scale for the Assessment of Positive Symptoms; BPRS = Brief Psychiatric Rating Scale; SD = standard deviation; ns = no significant group difference at $p < 0.05$, two-tailed.

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